Endocrinology
A Primer for Primary Care

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Objectives

- Review common endocrinology cases encountered by primary care
- Discuss appropriate treatment decisions
- To become comfortable managing primary care-related endocrine conditions

Common Endocrinology Cases in Primary Care

- Type 2 Diabetes
- Hypothyroidism
- Hypercalcemia
- Osteoporosis

DM-2 Case

- 48-year-old Caucasian male with uncontrolled DM-2
- BMI 36
- Kidney function is normal
- Currently receiving metformin 1000 mg BID, and glipizide 10 mg once daily
- A1C 9.1%
- What is the most appropriate plan of care?

Options

A) Increase glipizide to 10 mg BID

B) Add a new therapy

DM-2 Case 1

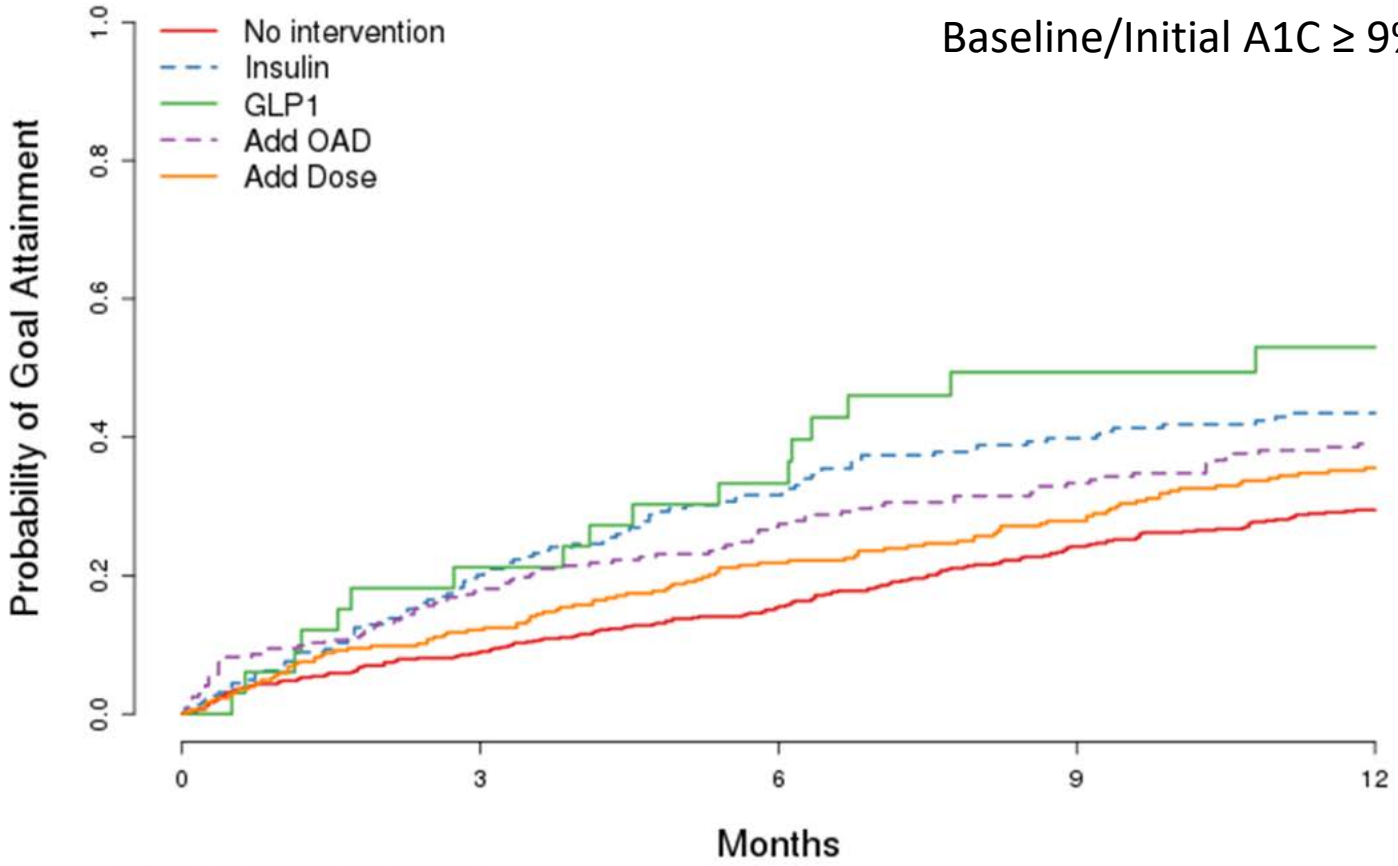
- Unlikely that increasing SFU will get A1C to goal, <7%

- It is even unlikely that adding an additional therapy, alone, will get the patient to goal
  - A1C lowering of 0.7% at most, on average, can be expected when adding a 3rd or 4th agent to improve glycemia

  - Choice of new therapy also matters

CCF Data (Submitted for Publication)

Baseline/Initial A1C ≥ 9%



Number of patients at risk					
643	586	524	458	404	No intervention
224	179	144	122	104	Insulin
33	26	21	14	12	GLP1
243	200	167	141	127	Add OAD
305	268	227	199	171	Add Dose

DM-2 Case #2

- 56-year-old African American female
- Weight 80 kg
- Kidney function good
- On Januvia 100 mg daily, metformin 1000 mg BID, and 50 units of insulin glargine
- A1C 7.8%
- What is the most appropriate next step?

DM-2 Case 2

A) Increase Lantus to 60 units

B) Add an SGLT2 inhibitor

C) Add glipizide

D) A&C

Correct Answer: B

- Why?
- Basal insulin dose already > 0.5 units/kg
- Need to look at her BG log to see if increasing basal is really a good/safe idea
- Adding SFU would only lower fasting BG further, which is not what is driving the residual A1C elevation

BG Log (mg/dL)

Day	pre-breakfast	pre-lunch	pre-dinner	bedtime
1	85	180	150	240
2	92	144	180	262
3	78	132	148	190
4	80			

- The problem is post-prandial hyperglycemia, particularly after larger meals (dinner)

- Adding an agent that will help with post-prandial control
  - -SGLT-2 inhibitor
  - -Consider switching the DPP-4 inhibitor to a GLP-1 receptor agonist
    - -A more potent incretin therapy

- Lower the dose of insulin glargine when start new medication
  - Fasting BG is already at goal, and BG is dropping too much while sleeping.
  - What happens if she doesn't eat much dinner and her BG is 130 mg/dL at bedtime?

Basal Insulin

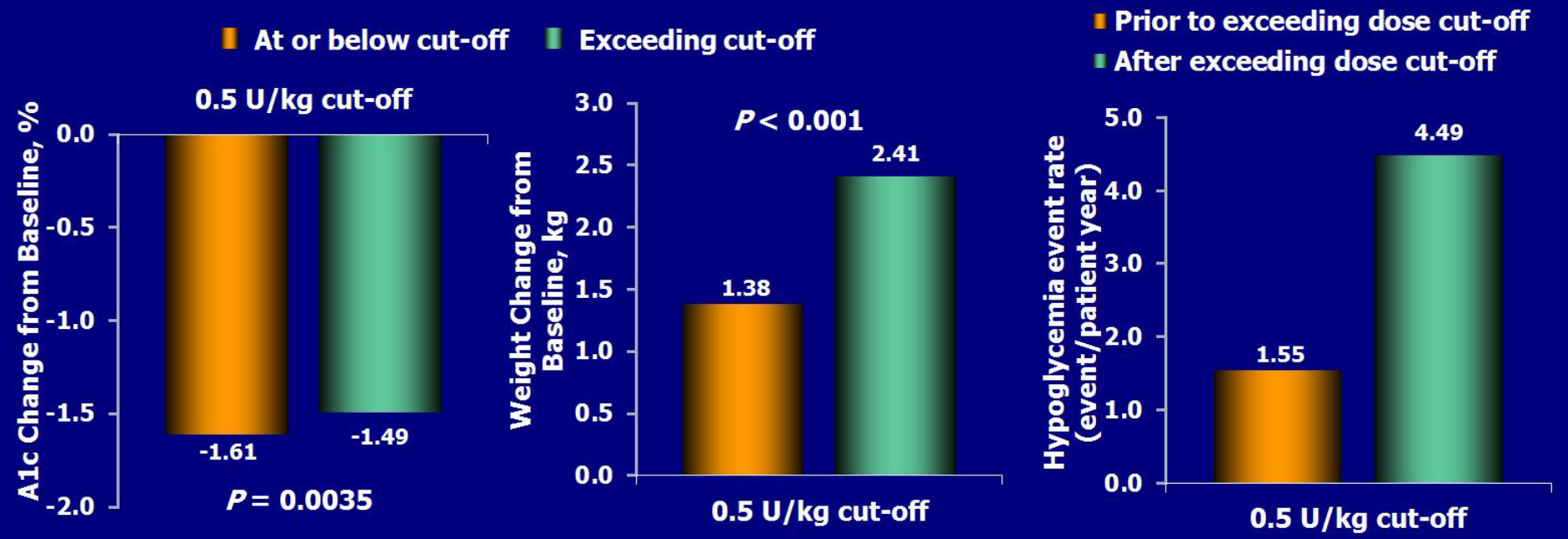
- Generally, once a patient's dose of basal insulin exceeds 0.5 units/kg, you need to reassess the plan-of-care

- If BG is dropping more than 50-70 mg/dL from HS to am, patient is at a high risk of hypoglycemia

- Studies evaluating higher basal insulin doses failed to show better glycemic control (A1C): 0.5 units/kg vs. 0.7 units/kg vs. 1 units/kg
  - More weight gain and hypoglycemia

Intensification of Basal Insulin Dose

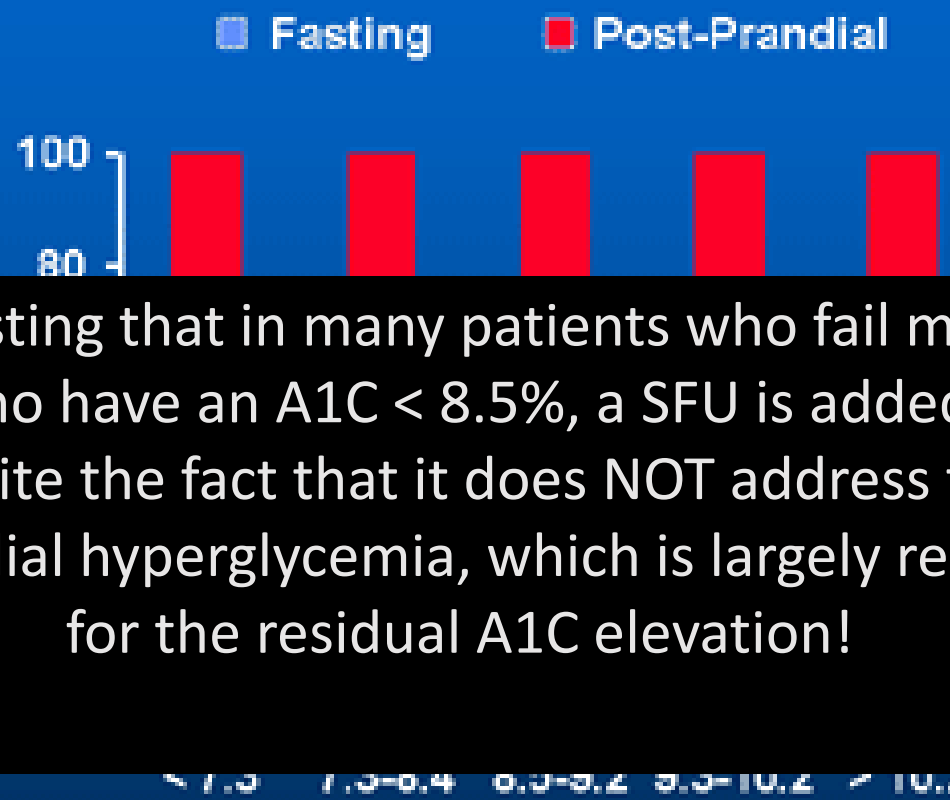
- A pooled analysis of data from 15 clinical trials of insulin glargine investigated 3 dose cut-offs
- Basal insulin dose beyond >0.5, >0.7 or >1.0 U/kg did not further improve glycemic control, and led to greater weight gain and higher likelihood of hypoglycemia



Study sponsored by Sanofi.

Reid T, et al. *Int J Clin Pract*. 2016. doi: 10.1111/ijcp.12747. [Epub ahead of print]

Contribution of Fasting & Post-Prandial Glycemia to A1C in T2DM



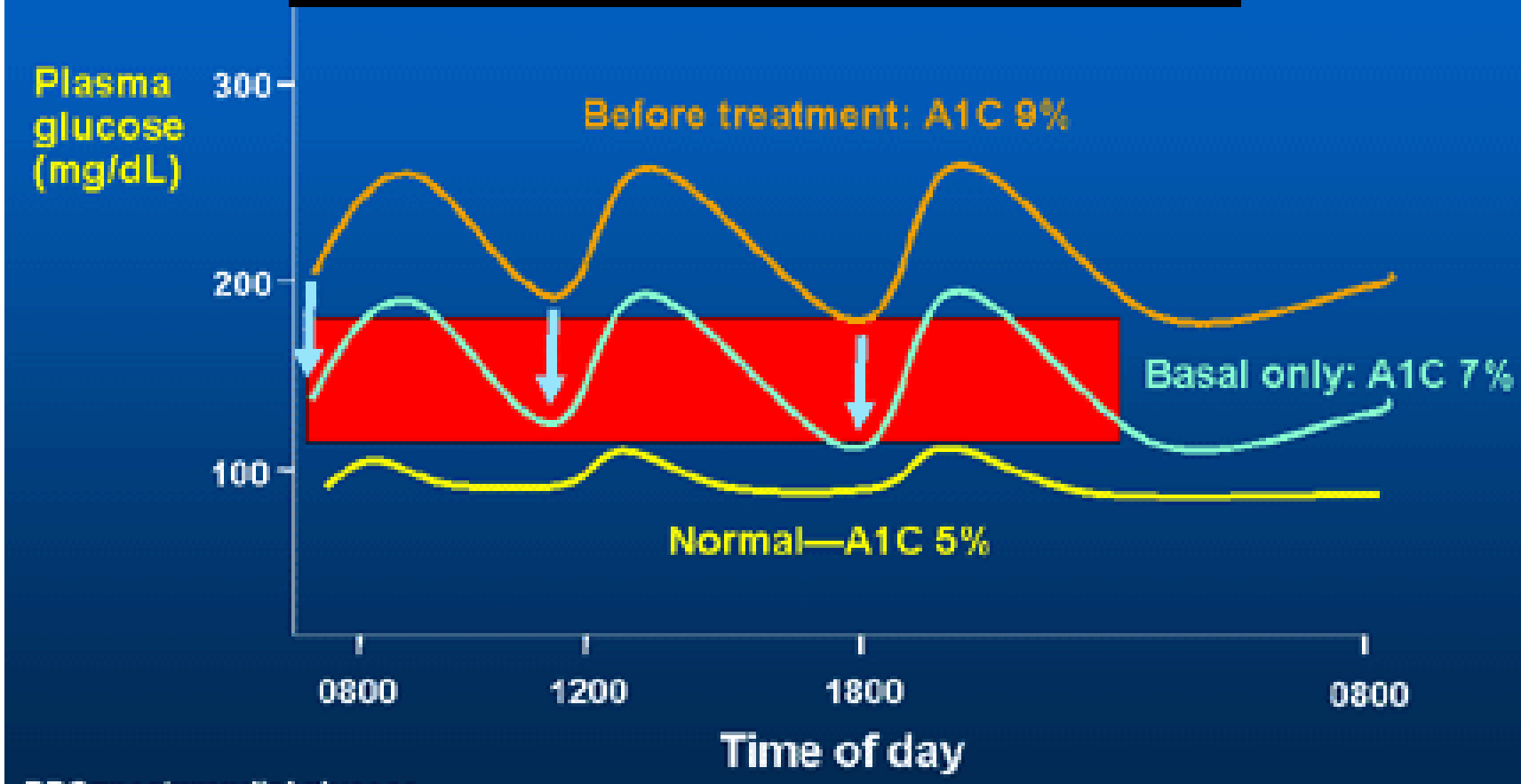
It is interesting that in many patients who fail metformin, who have an A1C < 8.5%, a SFU is added, despite the fact that it does NOT address the postprandial hyperglycemia, which is largely responsible for the residual A1C elevation!

Monnier L et al. *Diabetes Care*. 2003;26:881.

Glucose Profiles in Type 2 Diabetes

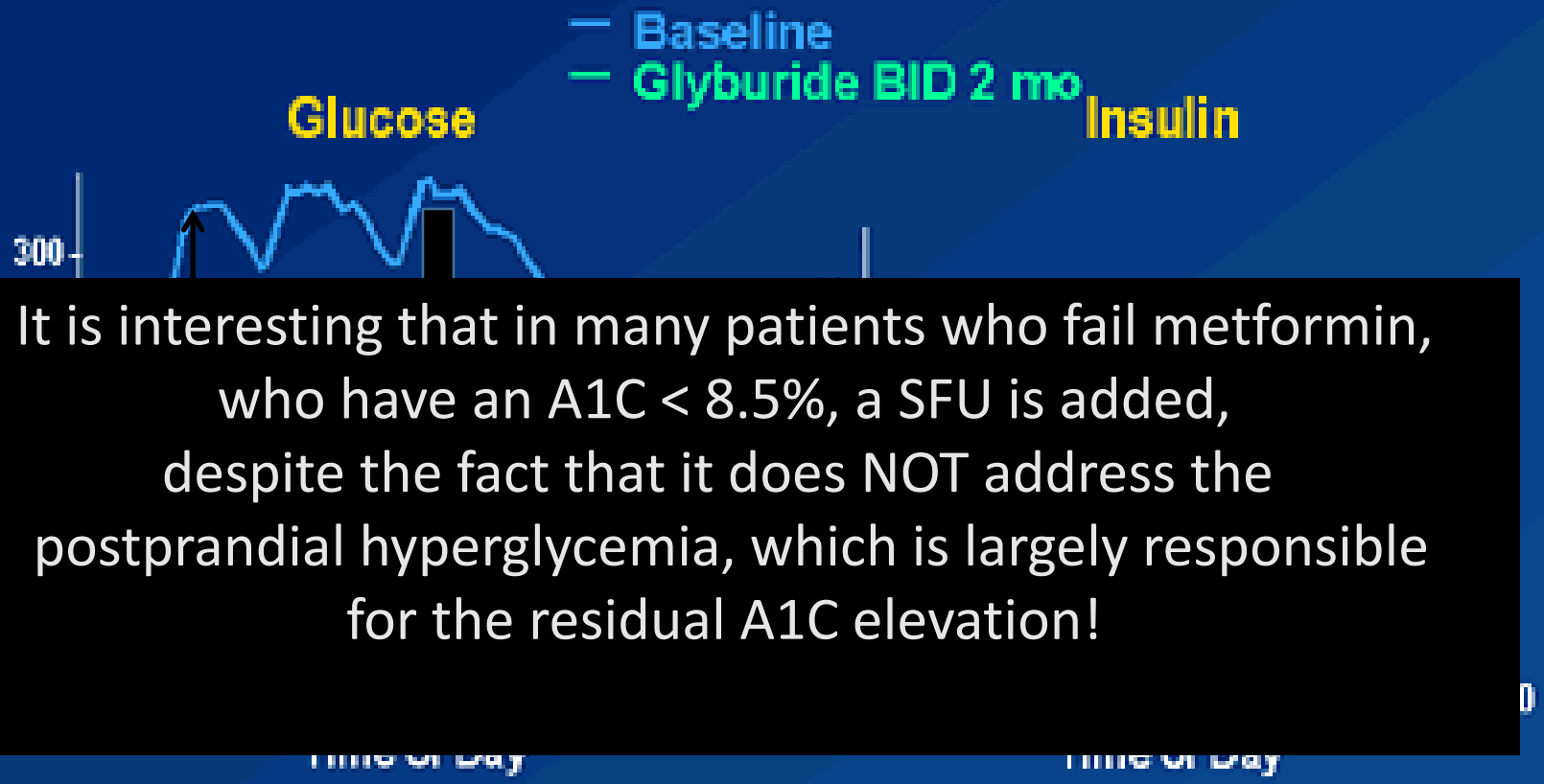
Correcting Basal vs Postprandial Hyperglycemia

"Shifting" down the plasma glucose, but wide glycemic excursions continue



PPG=postprandial glucose

Glyburide
No Effect on Postprandial Glycemic Increments



It is interesting that in many patients who fail metformin, who have an A1C < 8.5%, a SFU is added, despite the fact that it does NOT address the postprandial hyperglycemia, which is largely responsible for the residual A1C elevation!

Shapiro et al. J Clin Endocrinol Metab 1989;69:571-6

Hypothyroidism Case:

A 38-year-old Caucasian female
BMI 32
Otherwise healthy
Diagnosed with hypothyroidism a year ago
Takes 112 mcg of LT4

TSH – 2.197	(0.5-5.5)
Free T4 – 1.2	(0.9-1.8)
Free T3 – 2.9	(2.6-4.6)

Energy is not good, + fatigue; wants to try Armour thyroid…..

Primary Hypothyroidism-Common Causes

- Hashimoto’s Disease (Autoimmune)
- Post-surgical Hypothyroidism
- Post-RAI treatment (Graves, Toxic MNG)

Primary Hypothyroidism Diagnosis

- Elevated serum TSH in routine clinical practice

- Very few other disorders than can cause an elevated TSH
  - Lab interference (HAMA)
  - TSH secreting pituitary adenoma (rare)
  - Recovery from Euthyroid Sick Syndrome
  - Adrenal Insufficiency

Diagnosis, “per the experts”

- In most patients with symptoms or signs suggestive of hypothyroidism the serum TSH should be the initial test
  - ↑TSH, repeat the TSH with a serum free T4 to make the dx
    - Repeat ↑TSH and ↓FT4
      - Consistent with primary hypothyroidism, replacement therapy with T4 should be initiated
  - Repeat ↑TSH but normal range FT4
    - May indicate subclinical hypothyroidism
      - The decision about T4 replacement is made on a case by case basis and depends partly upon the degree of TSH elevation and symptoms reported by the patient

Diagnosis

- If TSH is within the normal reference range, but the patient has convincing symptoms of hypothyroidism
  - Repeat serum TSH and obtain free T4 to assess for central hypothyroidism (hypothalamic/pituitary disorder)

- Do not always assume that because the TSH is normal they do not have a thyroid problem
  - Rarely, central hypothyroidism can present with TSH values within the normal reference range, or even slightly elevated
    - Key is that the TSH level is clearly inadequate for the level of free T4
    - Example: Free T4 0.4 ng/dL (0.8-1.7), but TSH is 5.4 µIU/mL (0.5-5.5)
    - Almost always accompanied by other anterior pituitary abnormalities and symptoms

Some Patients have Persistent Symptoms Despite Adequate T4 Therapy

- Some patients have symptoms consistent with hypothyroidism despite adequate TSH and T4 levels

Saravanan P. Clin Endocrinol 2002; 57:577-85.
Walsh JP. Curr Opin Pharmacol 2002; 2:717-22.
Wekking EM. Eur J Endocrinol 2005; 153:747-53.

Some Patients have Persistent Symptoms Despite Adequate T4 Therapy

- Some of these patients ask for addition of T3 to the treatment regimen
  - Many of them have found claims of need for T3 on the internet
  - Some have friends whose doctors claim that only combination therapy works

It Is Not Your Thyroid (usually)!!!

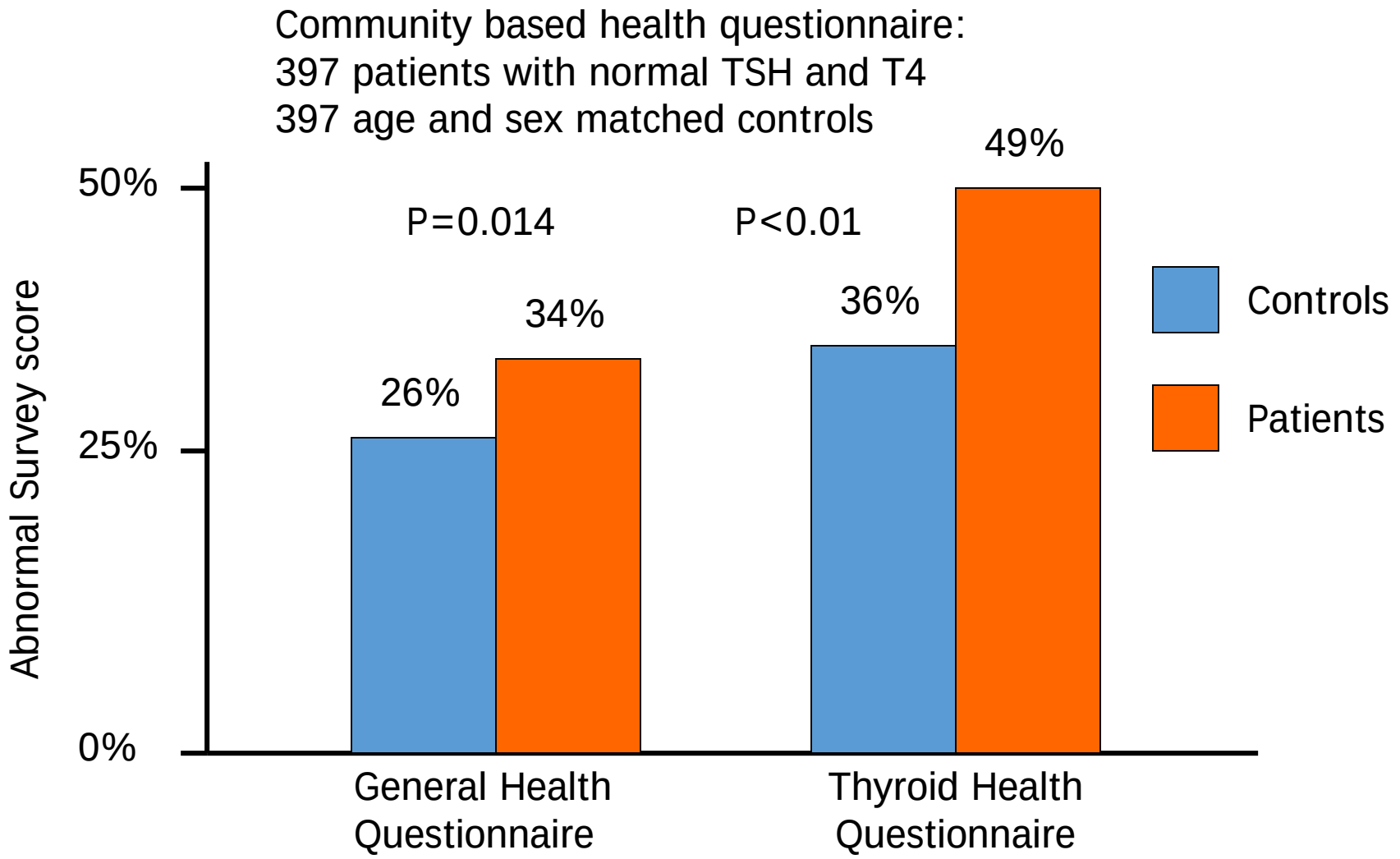
A significant number of these patients will have other conditions responsible for these residual symptoms

- Sleep disorders (Untreated OSA)
- Depression
- Medications causing fatigue
- Obesity
- Anemia
- Vitamin D deficiency
- Lack of EXERCISE!!!!
- Adrenal Insufficiency (rare)
  - Note, I did not mention Adrenal Fatigue!

- Treatment of these may lead to clinical improvement

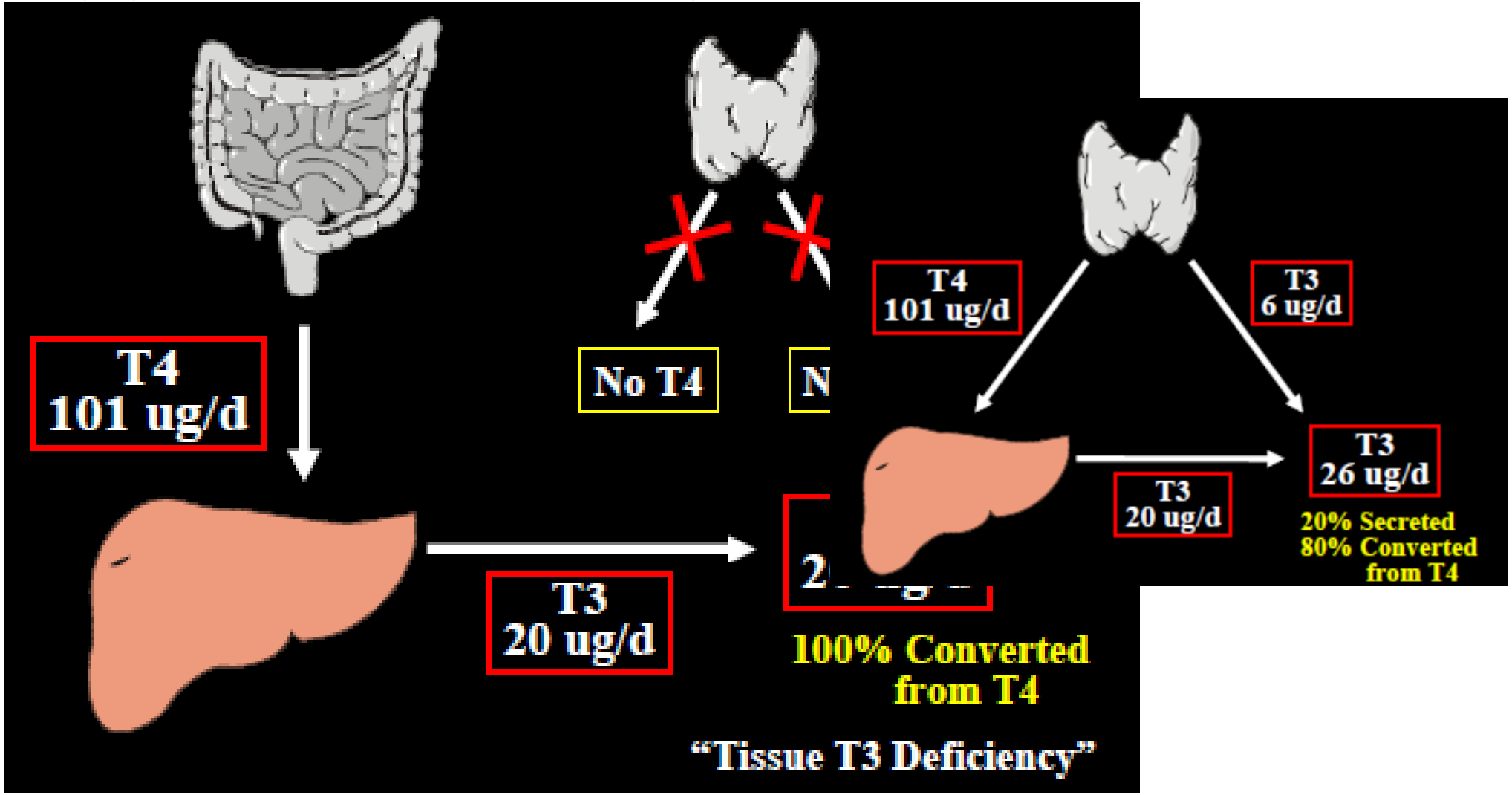
But, is there more to this story?

How many with persistent symptoms?



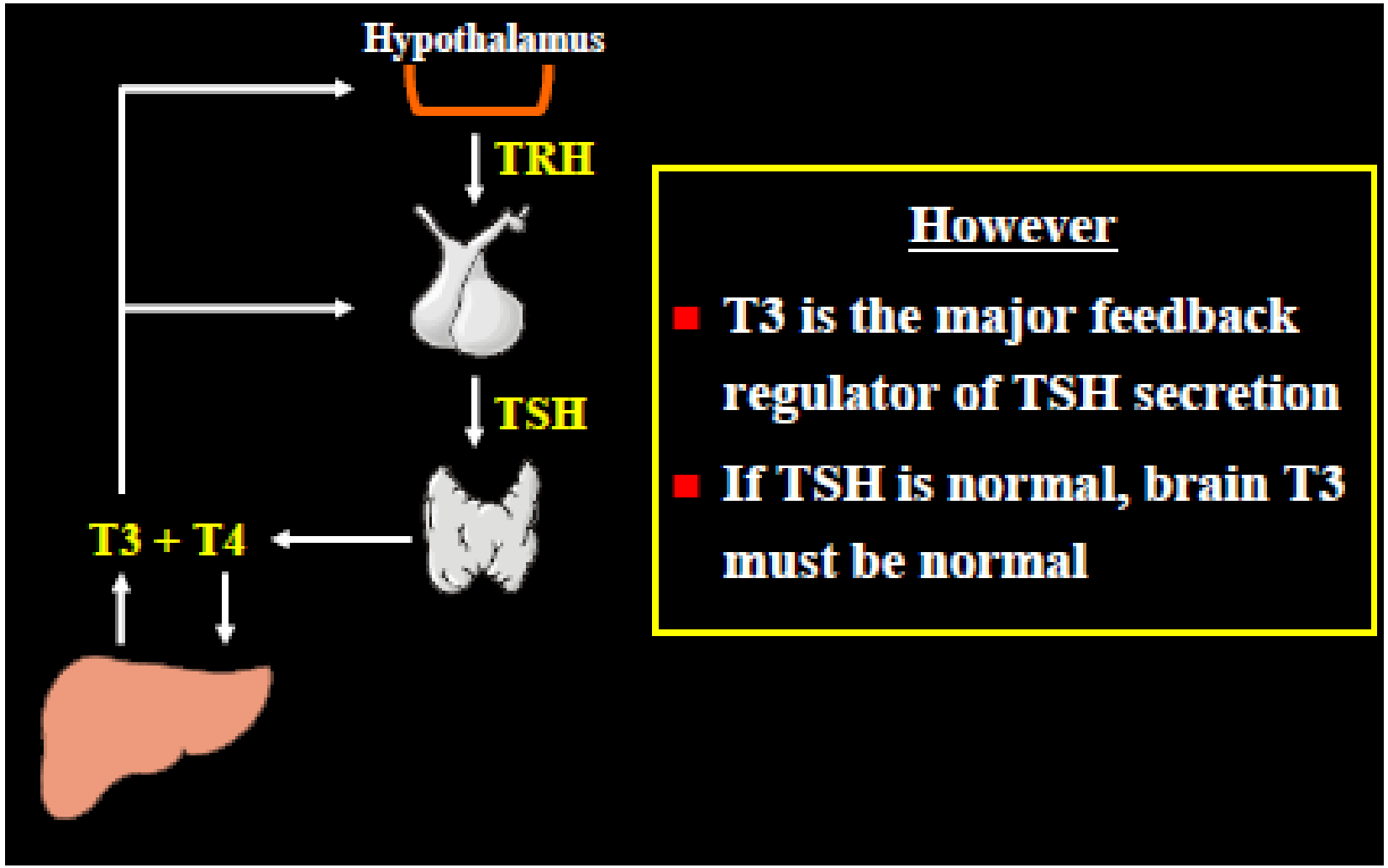
Saravanan P. Clin Endo. 2002:57:577-85.

T3 Therapy Needed Theory:



Pilo A, Am J Physiol 1990; 258:E715-26.

No T3 Therapy Needed Theory:



Pilo A, Am J Physiol 1990; 258:E715-26.

Early Randomized Controlled Trials of T4/T3 Combination Therapies

Study		Objective Benefit	Subjectove Benefit	T4/T3 Preference
Bunevicious 1999	Yes	Yes	Yes	
Walsh 2003		No	No	No
Sawka 2003		No	No	NA
Clyde 2003		No	No	NA
Siegmund 2004		No	No	NA
Saravanan 2005		No	No	NA
Escobar-Morreale 2005		No	No	Yes
Apelhof 2005		No	No	Yes
Rodriguez 2005		No	No	NA
Levitt 2005		No	No	NA
Regalbuto 2007		No	No	No
Slawik 2007 (Central)		No	No	NA

- **Escobar-Morreale 2005 Review:** **No benefit of T4/T3**
- **Grozinsky-Glasberg 2006 Meta-Analysis:** **No benefit of T4/T3**

Desiccated Thyroid Extract Compared With Levothyroxine in the Treatment of Hypothyroidism: A Randomized, Double-Blind, Crossover Study

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Objective: Our objective was to investigate the effectiveness of DTE compared with L-T_4 in hypothyroid patients.

Design and Setting: We conducted a randomized, double-blind, crossover study at a tertiary care center.

Patients: Patients (n = 70, age 18–65 years) diagnosed with primary hypothyroidism on a stable dose of L-T_4 for 6 months were included in the study.

Intervention: Patients were randomized to either DTE or L-T_4 for 16 weeks and then crossed over for the same duration.

Outcome Measures: Biochemical and neurocognitive tests at baseline and at the end of each treatment period were evaluated.

Results: There were no differences in symptoms and neurocognitive measurements between the 2 therapies. Patients lost 3 lb on DTE treatment (172.9 ± 36.4 lb vs 175.7 ± 37.7 lb, $P < .001$). At the end of the study, 34 patients (48.6%) preferred DTE, 13 (18.6%) preferred L-T_4, and 23 (32.9%) had no preference. In the subgroup analyses, those patients who preferred DTE lost 4 lb during the DTE treatment, and their subjective symptoms were significantly better while taking DTE as measured by the general health questionnaire-12 and thyroid symptom questionnaire ($P < .001$ for both). Five variables were predictors of preference for DTE.

Conclusion: DTE therapy did not result in a significant improvement in quality of life; however, DTE caused modest weight loss and nearly half (48.6%) of the study patients expressed preference for DTE over L-T_4. DTE therapy may be relevant for some hypothyroid patients. (*J Clin Endocrinol Metab* 98: 1982–1990, 2013)

Follow-up Testing

- TSH is all that is required unless there is something that does not make sense

- In most circumstances, there is very little information gained from checking FT4 or FT3 once the patients have started thyroid hormone therapy
  - Patients (and Dr. Google) will very frequently disagree
  - Do NOT let them convince you to order a reverse T3!

Hypercalcemia

- 44-year-old Caucasian female, DM-1, well controlled, otherwise healthy

Component	Latest Ref Rng & Units	7/7/2009	3/9/2010	7/16/2010
Calcium	8.6 - 10.0 mg/dL	10.3 (H)	10.0	10.3 (H)

2/4/2011	8/25/2012	3/9/2013	7/5/2013
10.3 (H)	10.2	10.2	10.1

12/14/2013	3/14/2014	1/16/2015	5/23/2015
9.6	9.7	9.6	10.8 (H)

9/26/2015	1/16/2016	5/6/2016
10.3	10.8 (H)	10.5

Typical Course

- “We will continue to monitor your calcium”
  - It is not magically going to get better
- Need to be more aggressive, evaluate/manage
- Check PTH, her PTH was 85 pg/mL (15-65) while calcium was 10.8 mg/dL (8.6-10)
  - Watch out for PTH values that remain in reference range in setting of hypercalcemia
    - “Inappropriately normal” PTH levels when the calcium is elevated
    - PTH normal range is only “normal” if calcium is normal
    - Should be suppressed if calcium is elevated
- She has primary hyperparathyroidism

Primary Hyperparathyroidism

- Primary hyperparathyroidism can occur at any age, but the great majority of cases occur in patients over the age of 50 to 65 years
- Women are affected twice as often as men
- In one study, the incidence of hyperparathyroidism was highest among blacks, followed by whites, Asians, Hispanics, and others

Griebeler ML et al. Bone 2015; 73:1.
Yeh MW et al. JCEM 2013; 98:1122.
Abood A, Vestergaard P. Dan Med J 2013; 60:A4567.

Who to refer for surgery?

Guidelines for surgery in asymptomatic PHPT: A comparison of current guidelines with the previous one*

Measurement¶	2008	2014
Serum calcium (>upper limit of normal)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
Skeletal	1. BMD by DXA: T-score <–2.5 at any site¶ 2. Previous fragility fracture△	1. BMD by DXA: T-score <–2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius¶ 2. Vertebral fracture by radiograph, CT, MRI, or VFA
Renal	1. eGFR <60 mL/min 2. 24-hour urine for calcium not recommended	1. Creatinine clearance <60 mL/min 2. 24-hour urine for calcium >400 mg/day (>10 mmol/day) and increased stone risk by biochemical stone risk analysis◇ 3. Presence of nephrolithiasis or nephrocalcinosis by radiograph, ultrasound, or CT
Age (years)	<50	<50

Patients need to meet only one of these criteria to be advised to have parathyroid surgery. They do not have to meet more than one.

PHPT: primary hyperparathyroidism; BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; CT: computed tomography; MRI: magnetic resonance imaging; VFA: vertebral fracture assessment; eGFR: estimated glomerular filtration rate; ISCD: International Society for Clinical Densitometry.

* Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible and in patients opting for surgery, in the absence of meeting any guidelines, as long as there are no medical contraindications.

¶ Consistent with the position established by the ISCD, the use of Z-scores instead of T-scores is recommended in evaluating BMD in premenopausal women and men younger than 50 years[1].

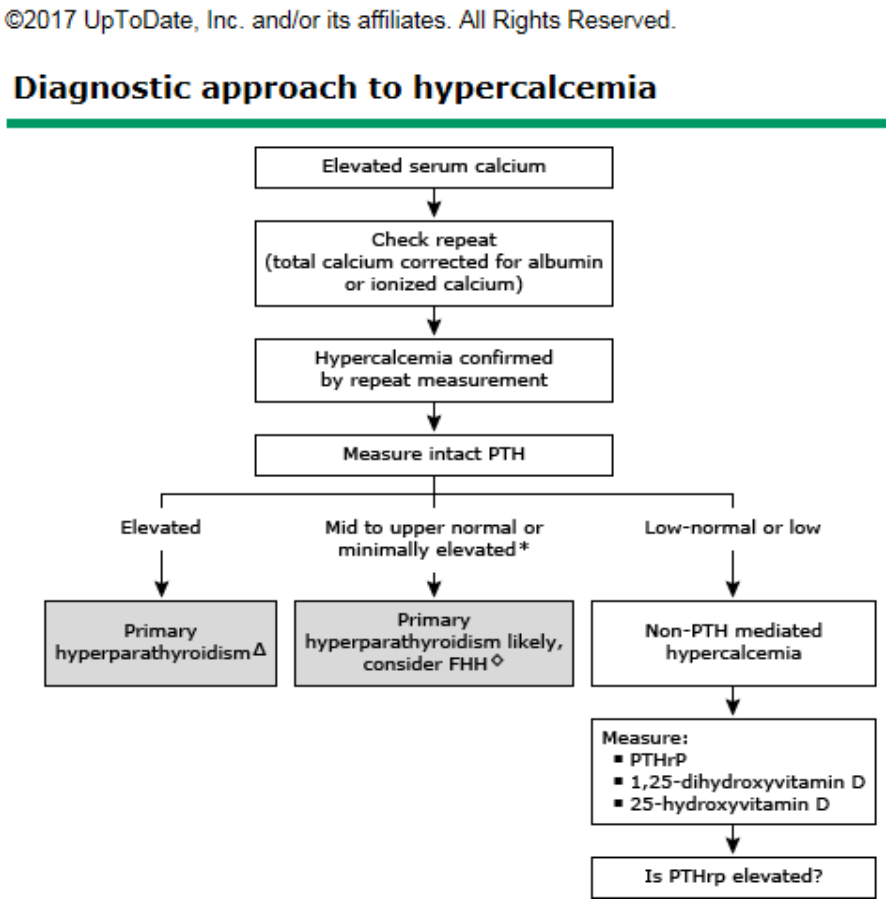
△ The history of a fragility fracture at any site would define someone as having a complication of PHPT, and thus, the individual would be automatically considered to be a surgical candidate.

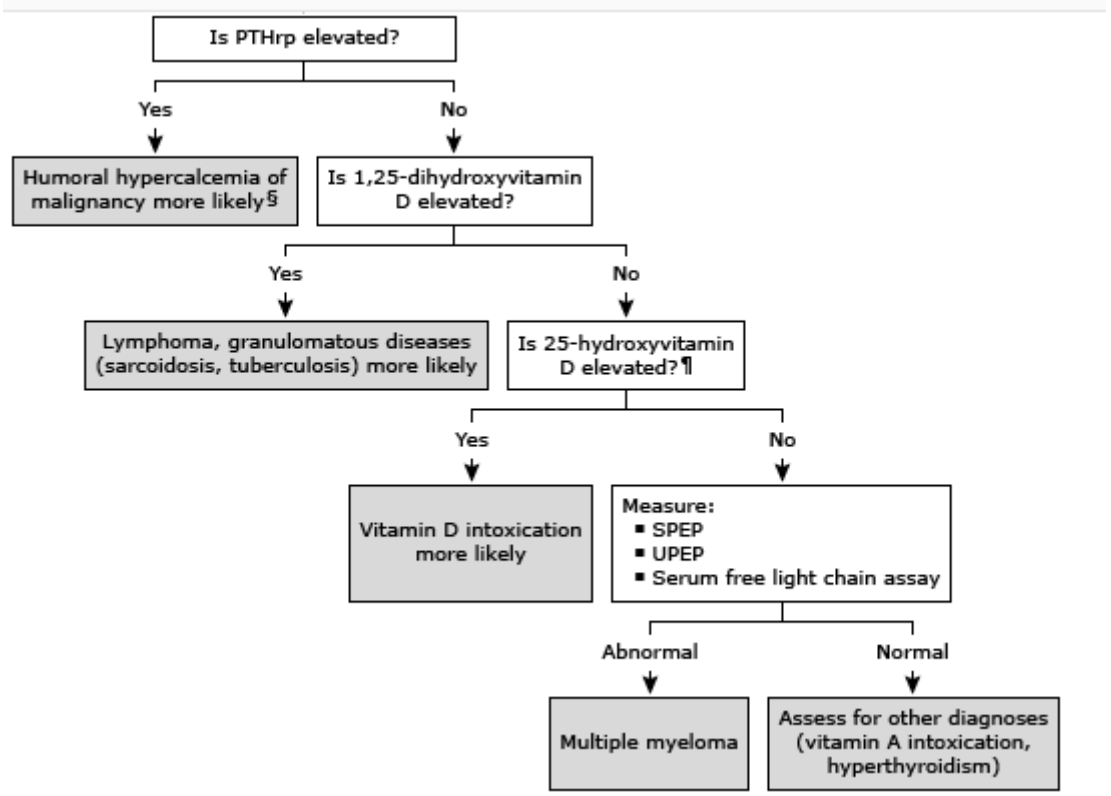
◇ Most clinicians will first obtain a 24-hour urine for calcium excretion. If marked hypercalciuria is present (>400 mg/day [>10 mmol/day]), further evidence of calcium-containing stone risk should be sought by a urinary biochemical stone risk profile, available through most commercial laboratories. In the presence of abnormal findings indicating increased calcium-containing stone risk and marked hypercalciuria, a guideline for surgery is met.

Reference:

1. *Lewiecki EM, Baim S, Langman CB, Bilezikian JP. The official positions of the International Society for Clinical Densitometry: perceptions and commentary. J Clin Densitom 2009; 12:267.*

Approach to Hypercalcemia





https://www.uptodate.com/contents/images/ENDO/51698/Diag_approach_hypercalcemia.gif

Osteoporosis:
68-year-old female

- Referred to you for a recent fracture
- She fell down trying to sit in a chair, fractured her T8 vertebrae
- Only medical condition is HTN treated with a beta blocker
- Started menstruation at the age of 13
- Menopause occurred naturally at the age of 51
- No family history of bone disorders

BMD

- Her DXA scan reported a T-score of -1.1
- She was told she had osteopenia and did not require therapy at this time
- Placed on vitamin D and calcium supplements
- She comes to see you for a 2nd opinion
- What should you tell her?

Does She Have Osteoporosis?

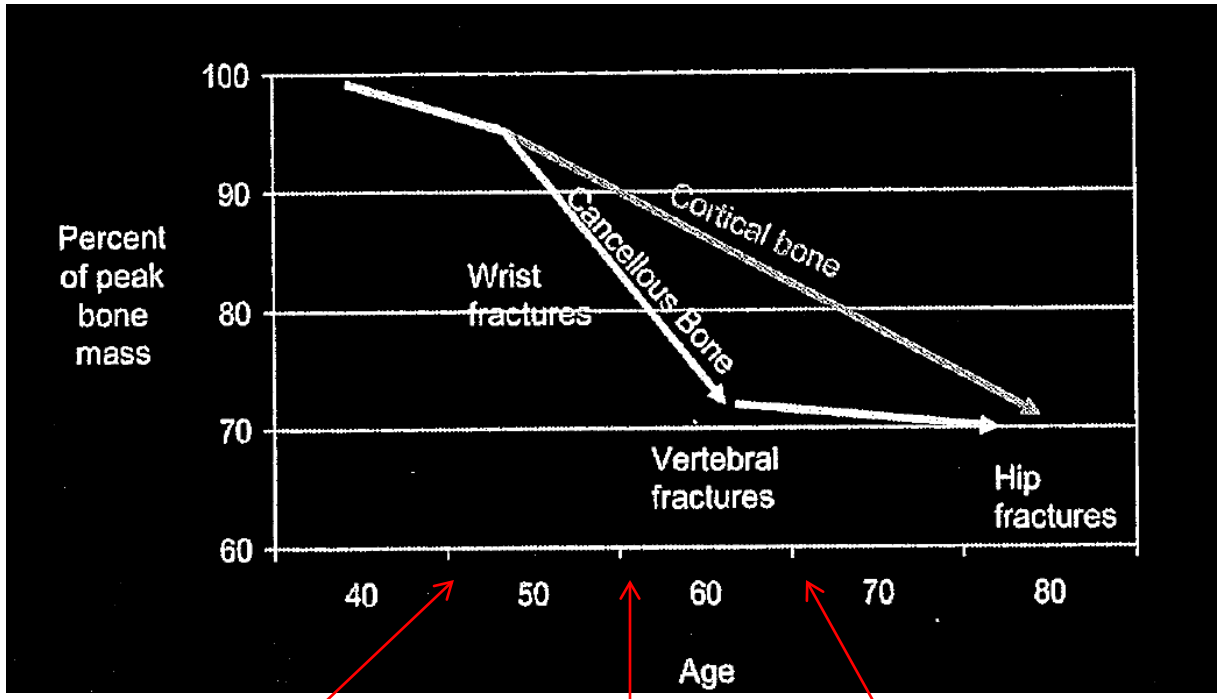
A) YES

B) NO

Osteoporosis

- Can be diagnosed irrespective of BMD and T-score
- The presence of a low trauma or fragility fracture is enough to make the diagnosis
  - A fracture resulting from the force of a fall from a standing height or less
  - Bone that breaks under conditions that would not cause a normal bone to break

Bone Loss



Wrist

Vertebral

Hip

Diagnosis & Treatment

- Osteoporosis
  - Calcium and Vitamin D supplementation
  - Bisphosphonate, or perhaps denosumab (Prolia)
  - Physical therapy
  - Addressing fall risks (banisters, rugs, etc.)

- BMD is only one component of bone strength
  - Bone quality is not as easy to assess
  - Presence of fracture, irrespective of BMD, reflects poor bone quality

Diagnosis

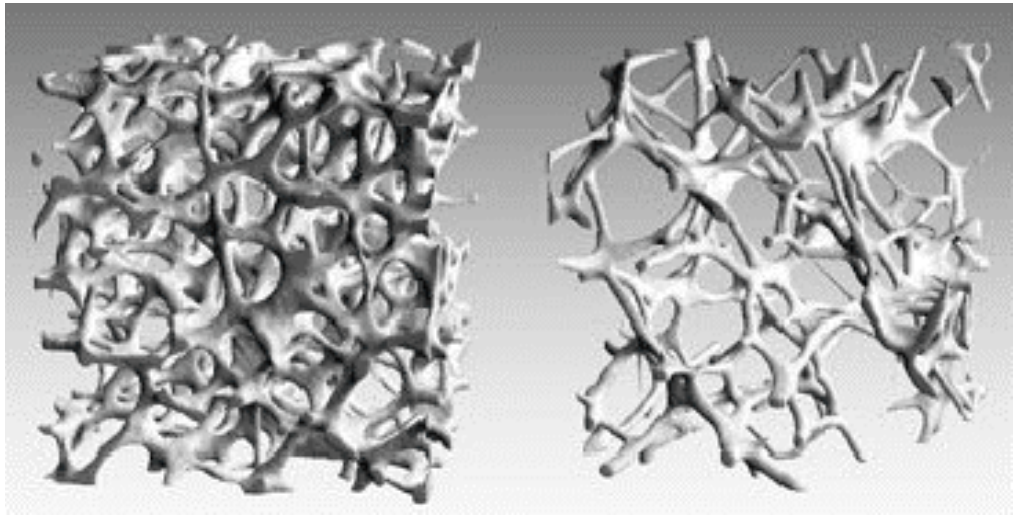
- Make sure any low trauma or fragility fracture is really not a pathological fracture
  - Tumor, infection, inherited bone disorder
  - Obtain X-ray and further labs if unsure!
- Careful history and physical
- Review of films

Osteoporosis Review

- A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture

- Bone strength reflects the integration of two main features
  - Bone Density and Bone Quality

Bone Quality



Healthy Unhealthy

Bone Strength = Bone Quality + Bone Density

↓ Age

Architecture
Turnover
Damage accumulation
Mineralization
Collagen quality

↓

g/cm2

hydroxyapatite

T-Score

- Number of SD the patient's BMD is above or below average BMD of **young** adult reference populations
  - Caucasian
- Can ONLY diagnosis osteoporosis via T-score alone in
  - Postmenopausal women
    -Menopausal transition
  - Men ≥50

T-Score

- Lumbar spine, total hip, or femoral neck
  - In certain circumstances, the 33% radius (AKA 1/3 radius) may be utilized
- ≥ -1.0 is normal
- Between -1.0 and -2.5
  - Low bone mass
  - Previously referred to as osteopenia
- ≤ -2.5 is osteoporosis

Z-Score

- Number of standard deviations the patient's BMD is above or below age-sex-matched mean reference value
    - Adjusted for self reported ethnicity

- Premenopausal women
- Males <50
- Children/Adolescents

Z-Score

≤-2.0 is “below the expected range for age”

>-2.0 is “within the expected range for age”

Diagnosis

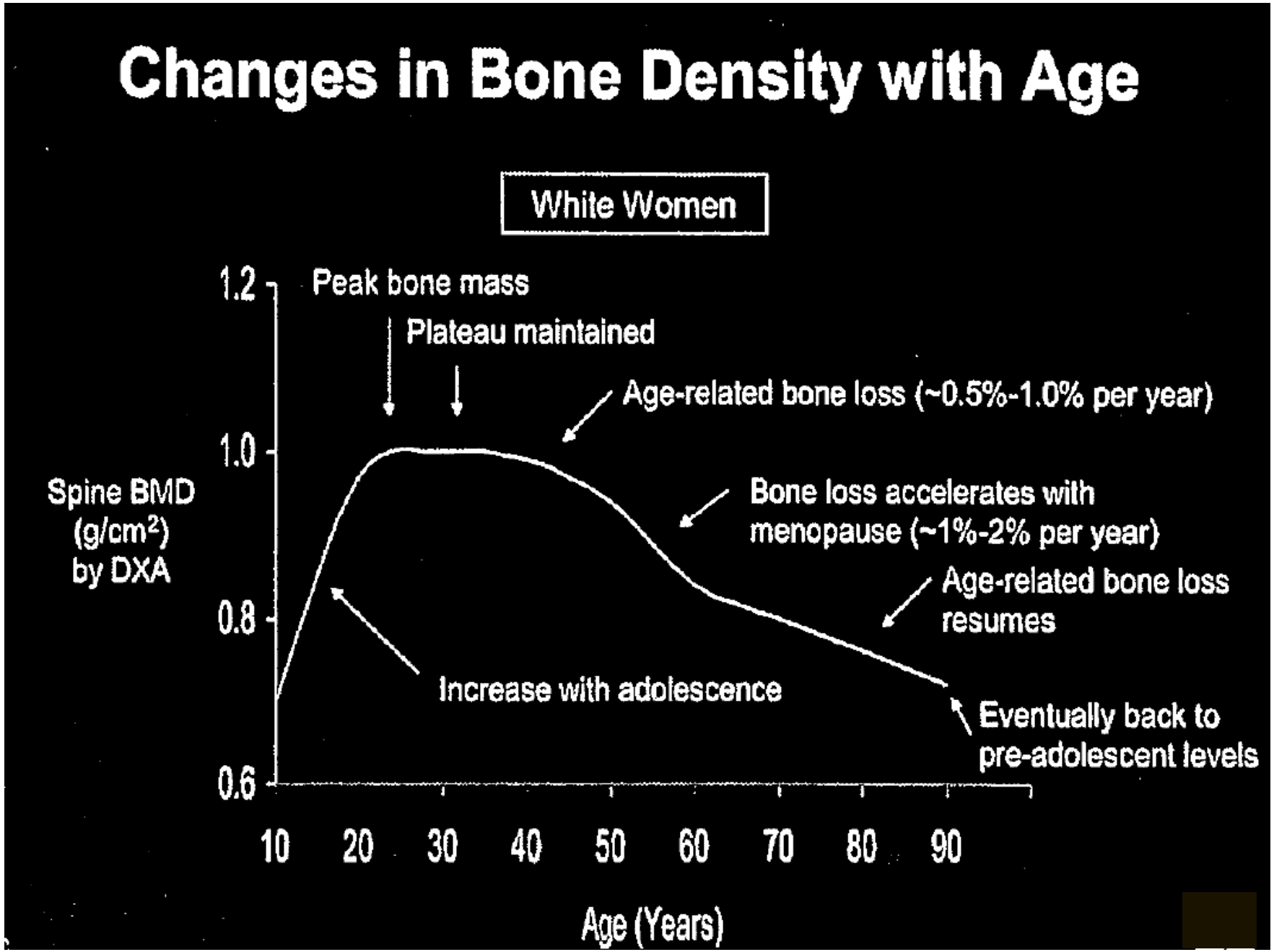
- Lowest T-score or Z-score is used to make the diagnosis
  - Use appropriate score in appropriate setting
  - T-score reporting for a 44-year-old male or premenopausal female is incorrect

- Often times the BMD reports incorrectly list two diagnoses:
  - “osteopenia at the lumbar spine and osteoporosis of the hip”

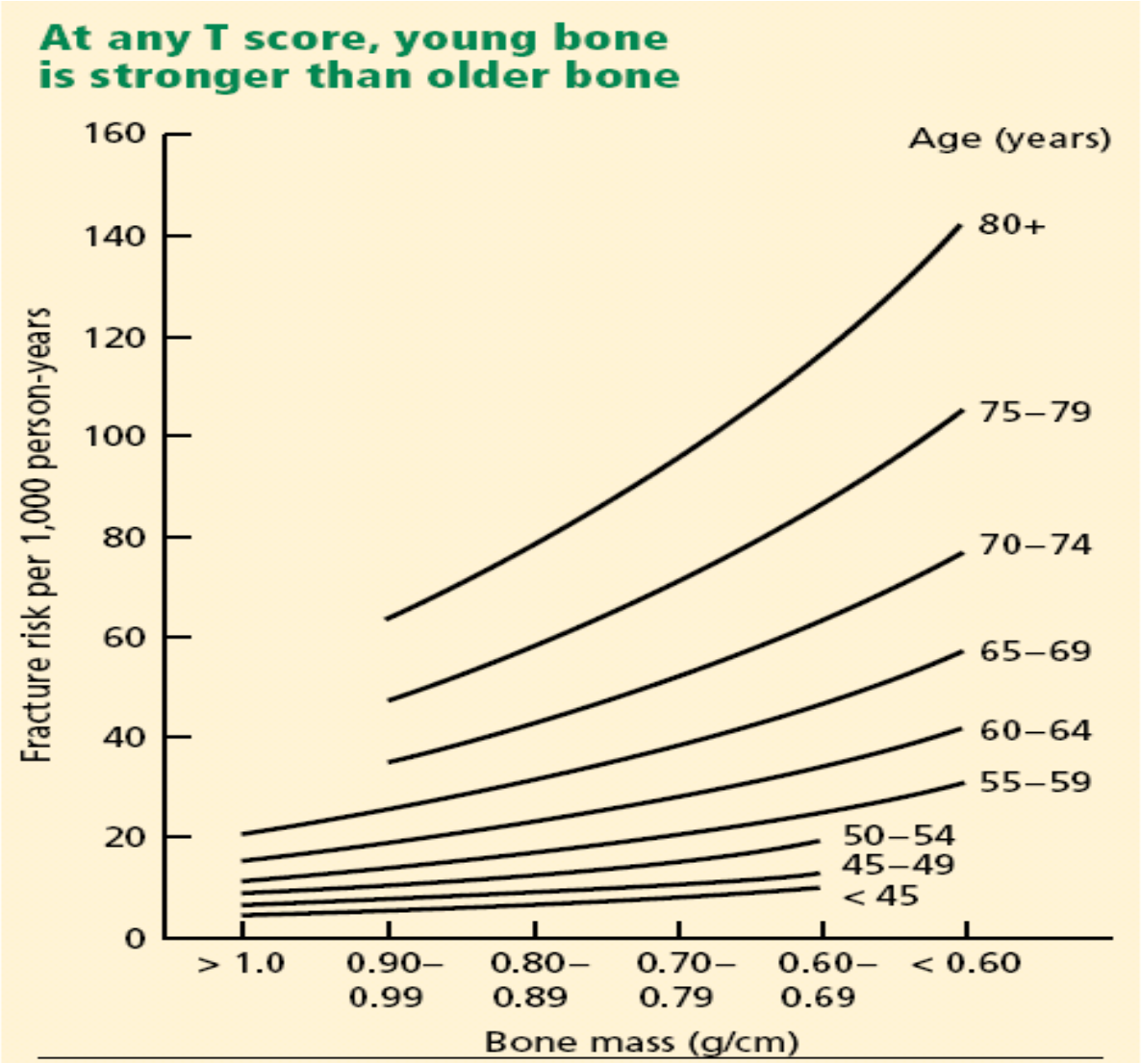
Low BMD

Does not necessarily mean “Bone Loss”

- **Determining bone loss requires prior BMD measurement**
- Low BMD can evolve in different ways:
  - Low peak bone mass
  - Low BMD followed by normal rate of loss
  - Normal peak BMD with accelerated loss
    - A single BMD can not distinguish these


Changes in Bone Density with Age
White Women
Peak bone mass
Plateau maintained
Age-related bone loss (~0.5%-1.0% per year)
Bone loss accelerates with menopause (~1%-2% per year)
Age-related bone loss resumes
Increase with adolescence
Eventually back to pre-adolescent levels
Spine BMD (g/cm²) by DXA
1.2
1.0
0.8
0.6
10 20 30 40 50 60 70 80 90
Age (Years)

Estimated incidence of fracture as a function of age and bone mass in 521 white women Followed for an average of 6.5 years



Hui SL et al. J Clin Inve st 1988; 81:1804–1809.

What to order?

Basic Testing

- CMP
  - Total protein, albumin, alk phos, LFTs, Cr
- Phosphorus
- CBC
- 25-OH Vitamin D
- 24 hour urine calcium/creatinine/sodium

What to order?

Further testing, if appropriate:

- Testosterone in males
- PTH
- TFTs
- Celiac disease Ab
- 4 hour urine free cortisol (and creatinine) or 1 mg DST
- SPEP/UPEP
- ESR, urine pH, serum bicarbonate
- Urine N-methylhistamine
- Bone turnover markers

Secondary causes, when to look beyond the basics?

- Men with osteoporosis
- Unexplained fracture
  - Fragility fracture with normal BMD
- Non-responder to therapy
- BMD loss that exceeds expected loss (LSC)
- High index of clinical suspicion

Least Significant Change?

- Did patient have repeat BMD completed on same machine?
  - Without a process called cross-calibration, you can **NOT** compare DXA results from different machines/manufacturers!
    - This is the biggest mistake made by health care providers!

- You also can **NOT** compare T-scores and infer bone loss or gain

Least Significant Change

- If done at same facility/machine, is this difference greater than the least significant change (LSC)?
- Lease Significant Change
  - There will be some difference from just error, differences in technician, etc.
  - LSC is based on precision error and reproducibility, which is largely determined by technician

Serial BMD

- Useful to determine whether treatment should be started on untreated patients
- Significant loss may be an indication for treatment (or further evaluation)
- Can also be used to monitor response to therapy or identify lack of response to therapy

When to repeat BMD?

- Interval varies, based on if expected change equals or exceeds the LSC
- Typically one year after initiation or change of therapy
- Longer intervals once therapeutic effect is established

Treatment

- Mainstays:
  - Oral bisphosphonates
  - IV yearly bisphosphonates (Reclast)
  - SC denosumab (Prolia), every 6 months

Thank You!

Questions ?????????