

Cases: Hypocalcemia and Hypophosphatemia

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#1 Hypocalcemia

- 59 yo woman
- Referred 2018 for low calcium and nonunion of fx
- Distal Tibial stress fx 2016, fixed locally 2017. Complicated by infection.
- Locally Osteop eval identified elevated PTH. 2 surgeries, last 12/2016.

- Meds
 - Calcitriol 0.5 mcg daily
 - Calcium citrate + D 315-250 mg-unit 2 TID
- Exam: BMI 37
 - chvostek's
 - Healed neck scar
- BMD LFN T-score -3.0

	Ref. Range	3/10/2018 09:34
Creatinine, S	Latest Ref Range: 0.6 - 1.1 MG/DL	1.3 (H)
Calcium, Total, S	Latest Ref Range: 8.9 - 10.1 MG/DL	7.0 (L)
Magnesium	Latest Ref Range: 1.7 - 2.3 MG/DL	1.5 (L)
Phosphorus (Inorganic), S	Latest Ref Range: 2.5 - 4.5 MG/DL	2.3 (L)
Parathyroid Hormone (PTH), S	Latest Ref Range: 15 - 65 PG/ML	35

Next step?

- A. Measure 24 hour urine calcium
- B. Increase calcitriol
- C. Add magnesium
- D. Measure 1,25 dihydroxyvitamin D
- E. Celiac serologies

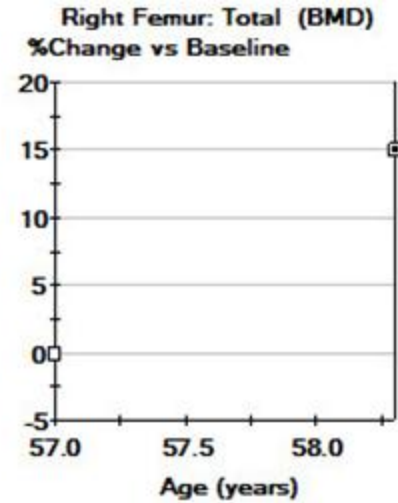
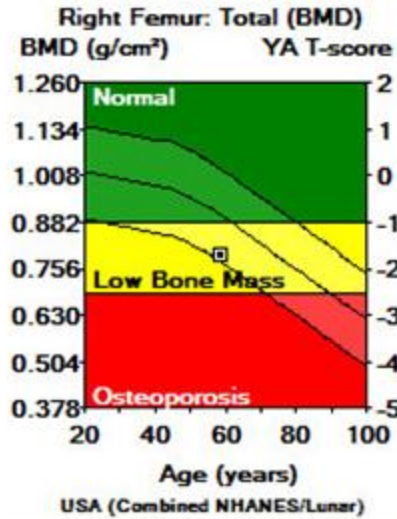
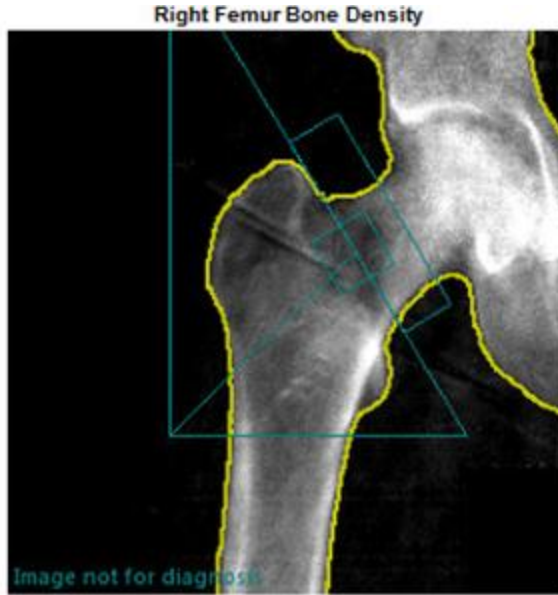
4/12/18

- Calcium 8.8 mg/dL (8.1-10.1)
- Phos 2.7 mg/dL (2.2-4.5)

Next step is

- A. Start a bisphosphonate
- B. Increase calcium supplement
- C. Measure 24 hour urine calcium
- D. No change to current regimen
- E. Add a thiazide type diuretic

- Abaloparatide 80 mcg daily initiated
- Returns 1 year later
 - Distal tibia is healed
 - Interim L femur fx no real trauma, R metatarsal fx



Densitometry: USA (Combined NHANES/Lunar)			
Region	BMD (g/cm ²)	Young-Adult T-score	Age-Matched Z-score
Neck	0.805	-1.7	-0.5
Total	0.796	-1.7	-0.9

COMMENTS:

Densitometry Trend: Total						
Measured Date	Age (years)	BMD (g/cm ²)	Change vs Previous (g/cm ²)	Change vs Previous (%)	T-score	Z-score
6/28/2019	58.3	0.796	0.104 *	15.0 *	-1.7	-0.9
3/7/2018	57.0	0.692	-	-	-2.5	-1.8

Ref. Range

6/28/2019 10:36

Calcium, Total, S Latest Ref Range: 8.6 - 10.0 mg/dL 8.4 (L)

Phosphorus (Inorganic), S Latest Ref Range: 2.5 - 4.5 mg/dL 2.0 (L)

Bone Alkaline Phosphatase, S Latest Units: mcg/L 39

Next step is

- A. Stop Tymlos
- B. Initiate PTH replacement therapy
- C. Increase calcitriol
- D. Increase calcium
- E. Measure PTH

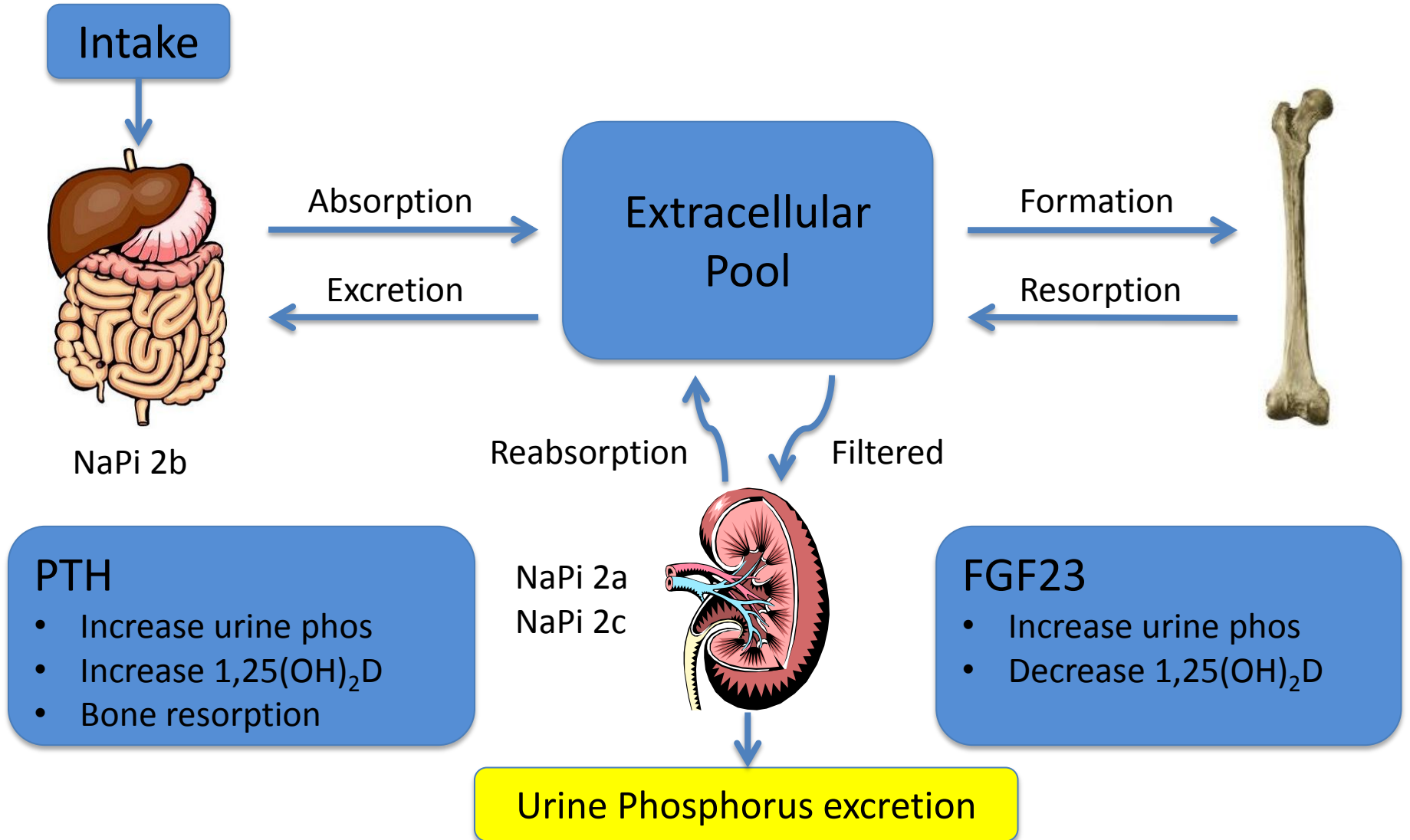
8/1/2019 15:30

Creatinine, S	Range: 0.59 - 1.04 mg/dL	0.97
Calcium, Total, S	Range: 8.6 - 10.0 mg/dL	8.5 (L)
Magnesium	Range: 1.7 - 2.3 mg/dL	1.9
Phosphorus (Inorganic), S	Range: 2.5 - 4.5 mg/dL	1.9 (L)
Parathyroid Hormone (PTH), S	Range: 15 - 65 pg/mL	50

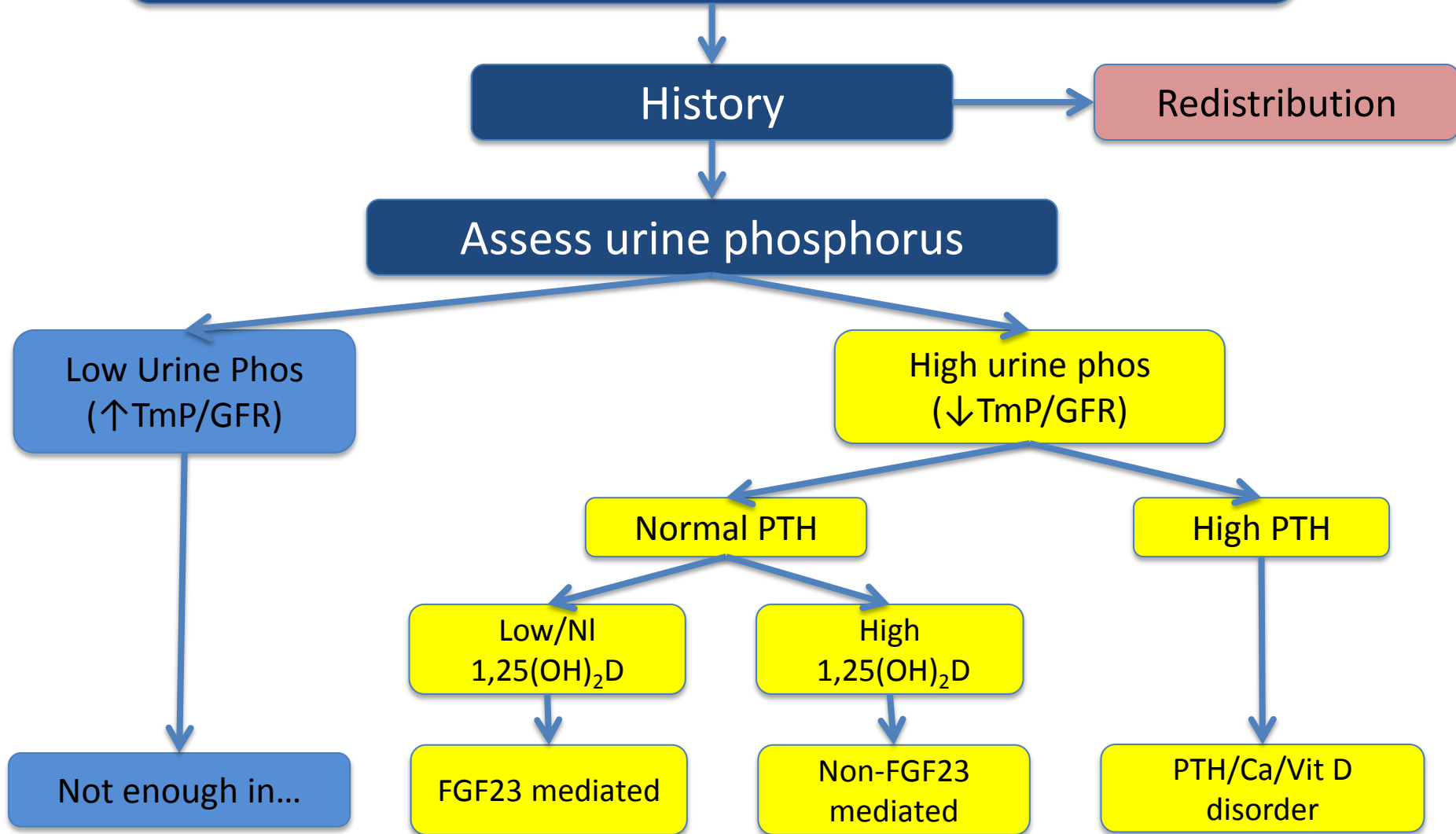
Next step is

- A. Increase calcium supplement
- B. Start phosphorus replacement
- C. Measure FGF-23
- D. Measure urinary phosphorus
- E. Measure 1,25 dihydroxyvitamin D

Phosphate Homeostasis



Low Serum Phosphorus

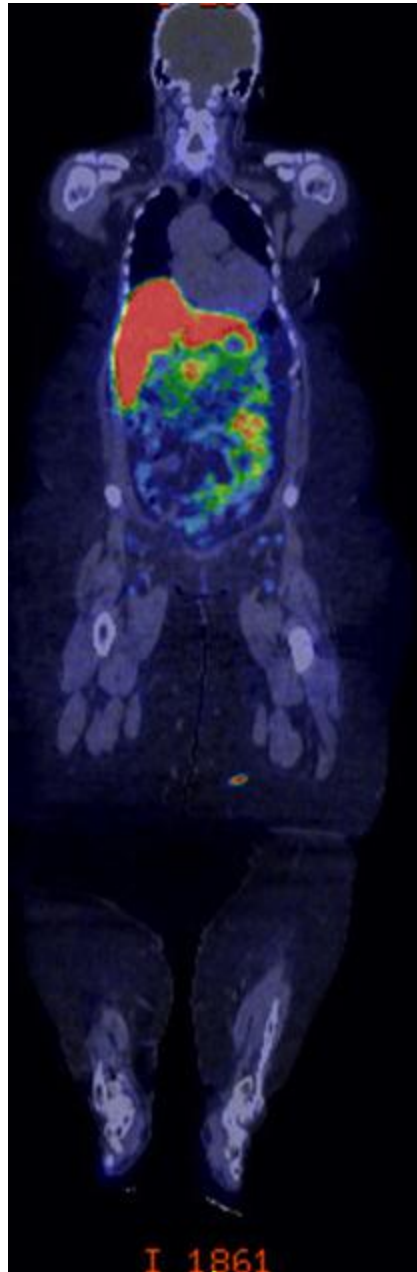


Fibroblast Growth Factor 23, P Range: ≤ 180 RU/mL 336 (H)

Next step is

- A. Measure urinary phosphorus excretion
- B. Dotate PET CT
- C. Whole body bone scan
- D. Whole body sestamibi scan
- E. Refer to oncology

Dotatate PET CT

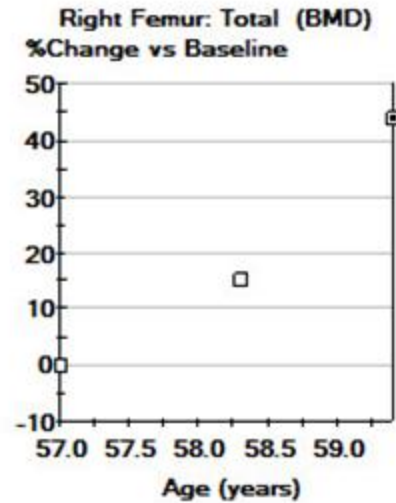
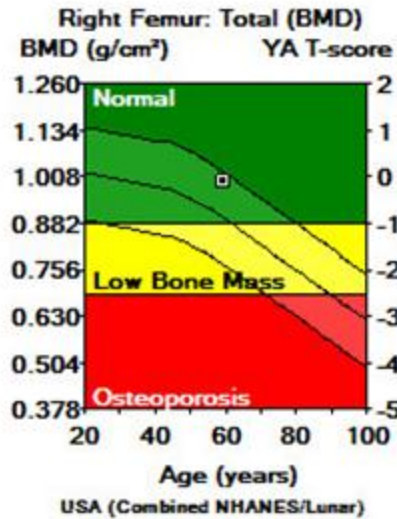
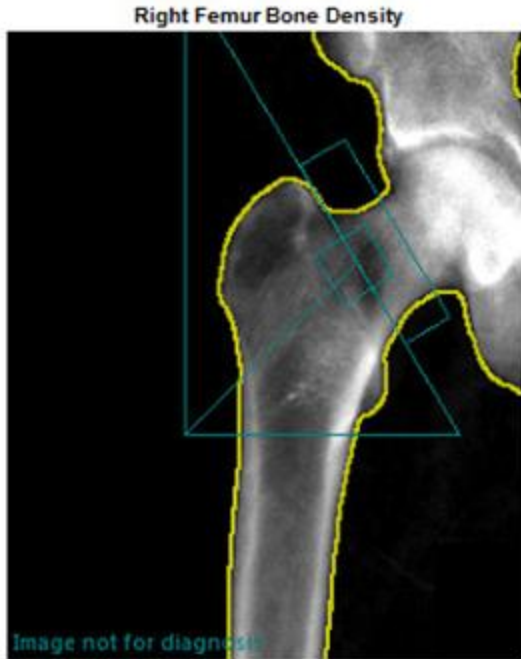


7 months after surgery

7/28/2020 09:46

Creatinine, S	Latest Ref Range: 0.59 - 1.04 mg/dL	0.98
Calcium, Total, S	Latest Ref Range: 8.6 - 10.0 mg/dL	9.0
Phosphorus (Inorganic), S	Range: 2.5 - 4.5 mg/dL	4.4
Parathyroid Hormone (PTH), S	Range: 15 - 65 pg/mL	42
Bone Alkaline Phosphatase, S	Units: mcg/L	18

2 years from first visit...



Densitometry: USA (Combined NHANES/Lunar)			
Region	BMD (g/cm ²)	Young-Adult T-score	Age-Matched Z-score
Neck	0.997	-0.3	0.9
Total	0.996	-0.1	0.8

COMMENTS:

Densitometry Trend: Total						
Measured Date	Age (years)	BMD (g/cm ²)	Change vs Previous (g/cm ²)	Change vs Previous (%)	T-score	Z-score
7/28/2020	59.4	0.996	0.200	25.1	-0.1	0.8
6/28/2019	58.3	0.796	0.104	15.0	-1.7	-0.9
3/7/2018	57.0	0.692	-	-	-2.5	-1.8

#2 eConsult Case

- 69 yo man admitted 3/24-3/30 with COVID 19 symptoms
- Took chloroquine prophylaxis for recent trip to Haiti and continued on this during hospital stay.
- eConsult to Endo 4/2 Re: hypocalcemia and hypoparathyroidism?

	1	2	3	4	5	6	7	8	9
	3/30/2020 0016	3/30/2020 0011	3/29/2020 0843	3/28/2020 0035	3/26/2020 0003	3/25/2020 2021	3/25/2020 2020	3/25/2020 0326	3/24/2020 2341
Chloride, S	100			98	99			101	
Chloride, P									99
Bicarbonate, S	28			27	29			27	
Bicarbonate, P									26
Anion Gap	9			10	11			10	
Anion Gap, P									11
Bld Urea Nitrog(BU...)	23			21	15			13	
BUN, P									14
Creatinine, S	1.03			1.06	0.97			1.06	
Creatinine, P									1.06
eGFR-Non Black	74 *			71 *	79 *			71 *	
eGFR Non-Black									71 *
eGFR-Black	85 *			82 *	>90 *			82 *	
eGFR Black									82 *
Calcium, Total, S	8.8			8.5 ▼	8.5 ▼			7.8 ▼	
Calcium, Total, P									8.4 ▼
Glucose, S	101			114	107			102	
Glucose, P									112
Bilirubin, Total, S	0.4		0.7				0.4	0.6	
Bilirubin, Direct, S	<0.2		<0.2				<0.2		
Alanine Aminotrans...	75 ▲		73 ▲				26	26	
Aspartate Aminotra...	66 ▲		63 ▲				35	37	
Alkaline Phosphata...	50		52				56	53	
Protein, Total, S	5.4 ▼		5.6 ▼				6.0 ▼	5.9 ▼	
Albumin, S	3.0 ▼		3.2 ▼				3.4 ▼	3.5	
Lactate									1.5
C-Reactive Protein...									51.7 ▲
Hospital Pri LD								292 ▲	
LIPIDS/CARDIAC RISK									
Creatine Kinase (C...	114								
OTHER CHEMISTRY									
25-Hydroxy D2	<4.0								
25-Hydroxy D3	21								
25-Hydroxy D Total	21 *								
Ferritin S							529 ▲		

3/30/20 PTH 12 pg/mL (15-65), 1,25 OH vit D <8.0 pg/mL (18-64)

Next step is

- A. Measure total calcium again now
- B. ionized calcium
- C. Request face to face consultation
- D. Nothing, it is related to chloroquine.
- E. Correct measured calcium for low albumin
- F. Start cholecalciferol and calcium supplement
- G. Start calcitriol and calcium supplement

Questions

- What is “normal” calcium in illness?
- What is the best test to assess calcium status?
- Is this hypoparathyroidism?

Calcium physiology

- 50% bound to negative molecules, such as protein and serum anions
- 50% ionized or free
- Ionized or free is biologically active and responsible for physiological functions

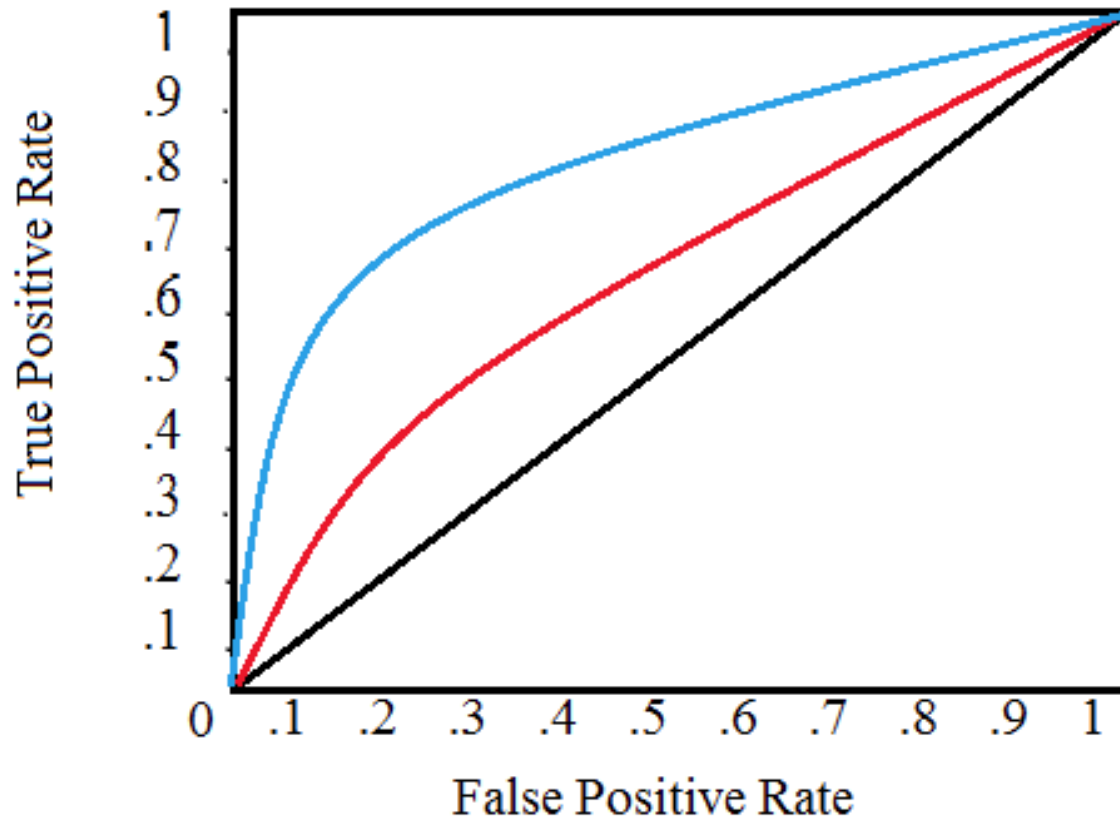
Payne formula 1973

- Attempts to “correct” for albumin and proteins in measuring total calcium
- Used methods to measure calcium and albumin that are not used today.
- Based on 200 patients
- Not validated by ionized calcium measurement

Problems with Albumin Corrected Calcium

- Binding constant of calcium to albumin changes with low albumin
- pH changes binding to albumin
- Poor performance in studies of hospitalized and outpatients compared with ionized calcium

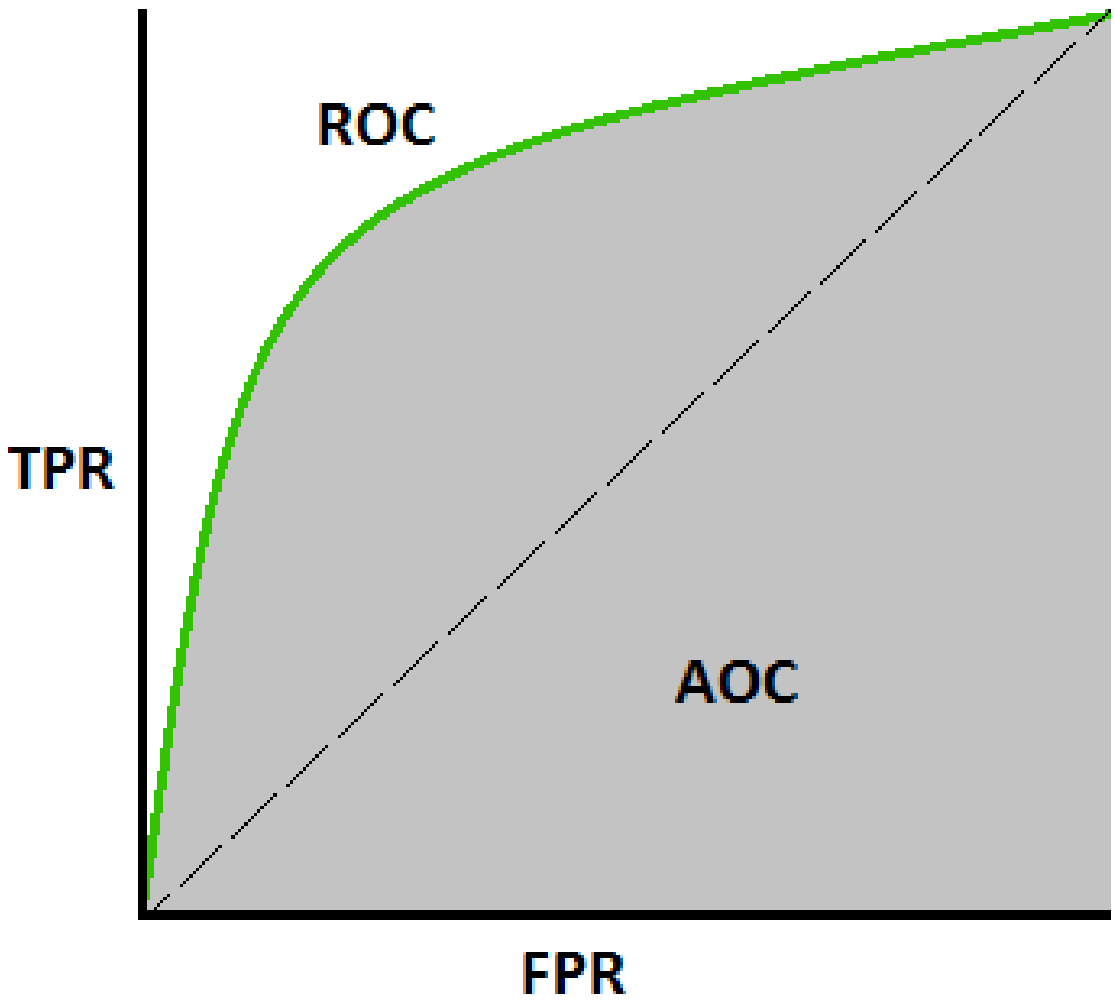
ROC for two tests. Which is more accurate?



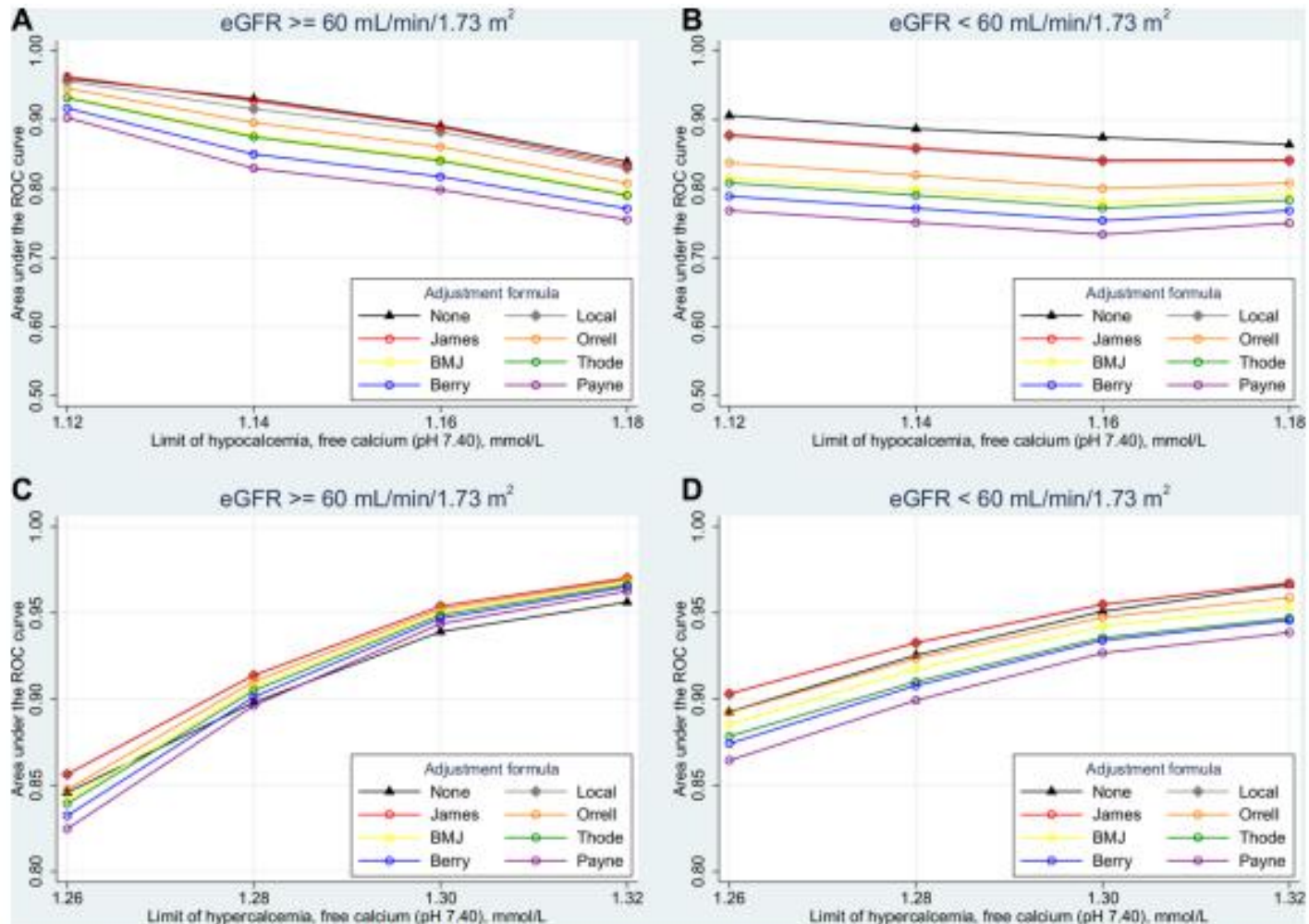
Receiver Operating Characteristic curve (ROC)

- A graphical plot that illustrates the diagnostic ability of a binary classifier system as its discrimination threshold is varied.
- Created by plotting the true positive rate against the false positive rate at various thresholds
- AUC (area under the ROC) is a measure of how well a parameter can distinguish between two diagnostic groups (diseased/normal) settings.

AUC



Adjusted Calcium Accuracy



Ionized Calcium

- pH dependent: higher binding of Ca to proteins when pH increased
- Is dynamic
 - Lactate creation due to continued cell metabolism
 - Loss of carbon dioxide during clotting
- Recommended samples for analysis: heparinized blood and anaerobically collected serum
- Time from collection to centrifugation to analysis can affect results

Conclusions

- Albumin adjusted total calcium is not superior to total calcium and maybe worse when albumin <3.0 or renal dysfunction or abnormal pH.
- Ionized calcium has pre-analytic, analytic sources of variation. Clinically significant?
- Low ionized calcium is common in critical illness. Adaptive or maladaptive?*
- Interpret result in the context of the clinical situation.

#3 Stones and low phos

- 22 yo man with htn and CKD and Ca stones referred for ? Hyperparathyroidism
- No fractures
- No family history of kidney stones

PE:

Obese, BMI 45 Height 182.3

Otherwise normal

- Labs:

May 2020

Ca 10.4 (8.6-10.4)

Alb 4.9

Phos 2.3 (2.5-4.5)

PTH 54 (15-65)

Creat 2.32

Jan 2020

10.0 (8.6-10.6)

1.8 (2.4-5.1)

46.6 (18.5-88.0)

2.41

- 24 hour urine: Ca 282 mg, Phos 1833, protein 2286 mg

Hypophosphatemia

- XLH
 - [PHEX](#) (phosphate-regulating endopeptidase on the X chromosome)
- ADHR
 - missense mutations in the gene encoding fibroblast growth factor 23 ([FGF23](#))
- ARHR
 - inactivating mutations in the [DMP1](#) gene
 - inactivating mutation in the [ENPP1](#) gene
 - mutations in the [FAM20C](#)

Hypophosphatemia with Hypercalciuria

- Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)
- Dent disease
- Idiopathic hypercalciuria

Dent's Disease

- X-linked recessive condition
- primary defect in the cells of the proximal renal tubule
 - proximal tubular solute-wasting,
 - hypercalciuria,
 - nephrocalcinosis,
 - kidney stones,
 - renal failure,
 - 25% of cases have rickets, evident from early childhood.