

Quadruple-H

A case of hyperparathyroidism, hyperthyroidism, hypercalcemia and hypertension

A case of persistent hypocalcemia

HOSP #	MRN63985901	WARD	Medical Ward
CONSULTANT	Dr. Heleen Vreede	DOB/AGE	51 year Female

Abnormal Result

Episode No

MRN

HPRN

Urgent

F

51 y

Clotted blood;EDTA blood;

F.N.

Alt

RN

Collection

09/03/2020

09:23

Hos

Groote Schuur Hospital wc GSH

021 404 9111

Received

09/03/2020

09:55

Wrd

G12 Medical Ward

404 3243 / 3547

Registered

09/03/2020

11:58

Doc

DR

ePR

Detail

Visit Test Set(s)

[A] SIND <A entry>

[E] PHONC <M entry> [VQ:PHONE

<SAZC001> [E] NA # <A entry> [V

<SAZC001> [E] K # <A entry> [VQ

<SAZC001> [A] UREA <A entry>

<SAZC001> [A] CRT <A entry>

<SAZC017> [E] CA # <A entry> [V

Update

Amend

Clear

<<

Notes

Graph

>>

Authorise

Fully Authorise

Cancel

Test Set	Staff Notes	Test Item	Result	Units	Normal Values	Previous Result 1	Previous Result 2	Previous Result 3	Previous Result 4	Previous Result 5
NA		Sodium	136	mmol/L	136 - 145	140 08/03/2020 08:50	140 06/03/2020 ?	139 24/01/2020 11:30	143 15/11/2019 10:25	140 23/08/2019 13
K		Potassium	3.8	mmol/L	3.5 - 5.1	4.7 08/03/2020 08:50	4.2 06/03/2020 ?	3.9 24/01/2020 11:30	5.3 15/11/2019 10:25	4.4 23/08/2019 13
UREA		Urea	8.8	mmol/L	2.1 - 7.1	9.7 08/03/2020 08:50	8.0 06/03/2020 ?	8.2 24/01/2020 11:30	7.5 15/11/2019 10:25	4.6 23/08/2019 13
CRT		Creatinine	102	umol/L	49 - 90	120 08/03/2020 08:50	95 06/03/2020 ?	134 24/01/2020 11:30	115 15/11/2019 10:25	54 23/08/2019 13
		MDRD formula	50	mL/min/1.73		41 08/03/2020 08:50	54 06/03/2020 ?	36 24/01/2020 11:30	43 15/11/2019 10:25	>60 23/08/2019 13
		CKD-EPI formula	55	mL/min/1.73		45 08/03/2020 08:50	60 06/03/2020 ?			
		Creatinine plus auto co	CM			CM 08/03/2020 08:50	CM 06/03/2020 ?	MDRD1 24/01/2020 11:30	MDRD1 15/11/2019 10:25	MDRD1 23/08/2019 13
CA	✓	Calcium	1.47	mmol/L	2.15 - 2.50	1.53 08/03/2020 08:50	1.55 06/03/2020 ?	1.44 24/01/2020 11:30	1.72 15/11/2019 10:25	1.80 23/08/2019 13
		Corrected calcium		mmol/L	2.15 - 2.55					
MG		Magnesium	0.53	mmol/L	0.63 - 1.05	0.54 08/03/2020 08:50	0.67 06/03/2020 ?	0.47 24/01/2020 11:30	0.52 15/11/2019 10:25	0.65 23/08/2019 13
PD4		Inorganic phosphate	0.94	mmol/L	0.78 - 1.42	1.01 08/03/2020 08:50	0.99 06/03/2020 ?	1.14 24/01/2020 11:30	1.53 15/11/2019 10:25	1.40 23/08/2019 13
SIND		Serum haemoglobin inc	0			0 08/03/2020 08:50	0 06/03/2020 ?	0 24/01/2020 11:30	0 15/11/2019 10:25	0 23/08/2019 13
		Serum bilirubin index	0			0 08/03/2020 08:50	0 06/03/2020 ?	0 24/01/2020 11:30	0 15/11/2019 10:25	0 23/08/2019 13
		Serum lipaemia index	0			0 08/03/2020 08:50	0 06/03/2020 ?	0 24/01/2020 11:30	0 15/11/2019 10:25	0 23/08/2019 13
		Serum haemoglobin va	16.00			13.00 08/03/2020 08:50	15.00 06/03/2020 ?	7.00 24/01/2020 11:30	12.00 15/11/2019 10:25	7.00 23/08/2019 13
		Serum bilirubin value	0.00			0.00 08/03/2020 08:50	0.00 06/03/2020 ?	0.00 24/01/2020 11:30	0.00 15/11/2019 10:25	0.00 23/08/2019 13
		Serum lipaemia value	2.00			12.00 08/03/2020 08:50	13.00 06/03/2020 ?	0.00 24/01/2020 11:30	8.00 15/11/2019 10:25	9.00 23/08/2019 13
PHONC		Date phoned				24/01/2020				

Total calcium of 1.47 mmol/L (2.15 – 2.50)

Presenting Complaint

The patient has been having persistent hypocalcemia despite supplementation with calcium.

History

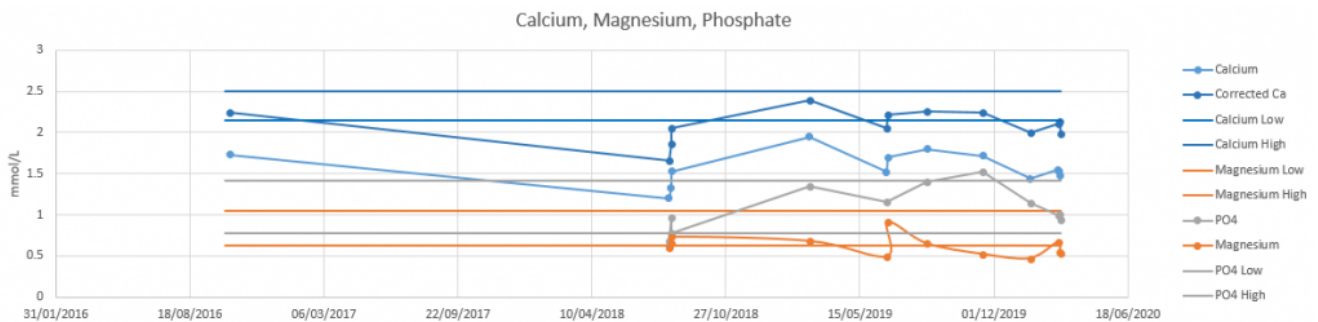


Figure 1 – Illustration of the patient's CMP over time:
Calcium: blue; Magnesium: orange; Phosphate: grey
Reference ranges are the horizontal lines without dotted markers

Examination

Not available.

The typical findings in a patient with true hypocalcemia (low ionised calcium) are

Trousseau's sign

Chvostek's sign

Laboratory Investigations

Arguably, the first important consideration in patients with low calcium is the albumin. The patient had a mean albumin of 12 g/L, significantly lower than normal (40-50g/L). Arguably, the calcium can be corrected with the well known Payne's formula to then be $1.47 + (0.02 \times (40-12)) = 2.03$ mmol/L:

$$\text{Albumin-adjusted calcium (mmol/L)} = \text{total calcium (mmol/L)} +$$

0.02 [40 – albumin (g/L)])

Payne RB, Little AJ, Williams RB, Milner JP. Interpretation of serum calcium in patient with abnormal serum proteins. *Br Med J*. 1973;4:643-646. DOI: 10.1136/bmj.4.5893.643. ([View](#))

Measurement of serum intact parathyroid hormone (PTH) should be performed in all patients with hypocalcemia; it is the most valuable laboratory test for determining the etiology of hypocalcemia:

	2019/11/15	2019/06/28	2018/08/03
PTH (pmol/L)	21,8 H	15,5 H	25,8 H

Reference interval: (1.6-6.9 pmol/L)

Vitamin D

	09/09/2020	15/11/2019	03/08/2018
Total Vitamin D (25-OH VitD)	20.5 nmol/L	45.4 nmol/L	23.2 nmol/L

Guidelines for assessment of Vitamin D status:

<30 nmol/L <12 ng/mL Deficient

30-50 nmol/L 12-20 ng/mL Insufficient

>50 nmol/L >20 ng/mL Sufficient

125-150 nmol/L 50-60 ng/mL Safe upper limit

Reference: Revised South African Clinical Guideline for the diagnosis and management of osteoporosis (NOFSA 2017), endorsing the institute of Medicine Dietary Reference intakes for calcium and vitamin D (2010). Note regarding conversion of units:

Divide result in nmol/L by 2.496 to convert to ng/mL

Multiply result in ng/mL by 2.496 to convert to nmol/L

Other Investigations

Anti-Tissue Transglutaminase antibodies: **Negative**: repeated 3 months apart, with sufficient IgA levels in the serum): 0.9 & 0.8 U/mL (EliA c/o: 6.9)

Anti-Gliadin antibodies: **Equivocal**: 7.8 & 9.6 U/mL (EliA c/o: 6.9)

Anti-endomysial antibodies: **Negative**

HLA-DQ2: **Positive**

HLA-DQ8: **Negative**

Final Diagnosis

Hypocalcemia likely due to malabsorption (telangiectasia stated by the clinicians).

#Intestinal lymphangiectasia
#Protein losing enteropathy
#Osteoporosis secondary to osteomalacia
#Prev Tb adenitis
#Last admission 6-18 March 2020 with diarrhoea, poor nutrition and renal impairment
Now presented with protein losing enteropathy and AKI as well as concerns for sepsis with a raised CRP. Presented with abdominal distension, leg swelling and diarrhoea this admission. Patient receiving NG tube feeds and will be discharged home with a NG tube. Also received IVI albumin in the ward
Today: Pt doing well
Vitals stable and clinically stable upon discharge

Discharge medication:
FUROSEMIDE Tablets, 40mg Daily Orally, 1 month CALCIUM CARBONATE Powder, 2T 12 hourly Orally, 1 month VITAMIN D (CALCIFEROL) Tablets, 50000IU Weekly Orally, 1 month MAGNESIUM CHLORIDE Powder, 2T 12 hourly Orally, 1 month
FERROUS SULPHATE Crystals, 200mg Daily Orally, 1 month FOLIC ACID Tablets, 5mg Daily Orally, 1 month VITAMIN B1 (THIAMINE) Tablets, 100mg Daily Orally, 1 month OMEPRAZOLE Tablets, 20mg Daily Orally, 1 month TRAMADOL Capsules, 50mg 3 times daily Orally, 1 month

Take Home Message

According to International guidelines the following association is expected for patients with Coeliac Disease:

Positive for HLA-DQ2 (HLA-DQA1*05, DQB1*02)

Positive for HLA-DQ8 (HLA-DQA1*03, DQB1*03:02)

Considering the fact that the albumin was high with an increased PTH, the calcium very likely was physiologically

also low (bioactive Ca). The Payne's formula also failed to correct the calcium to the normal reference range.

[Cumulative History:Download](#)

The Vitamin D conundrum

HOSP #		WARD	F22 Orthopaedics Ward
CONSULTANT	Dr. Jody Rusch	DOB/AGE	42 Y Female

Abnormal Result

Total Vitamin D of 27.1 nmol/L on 18 March 2020.

Total Vitamin D of 65.4 nmol/L on 01 April 2020.

Presenting Complaint

Patient had a low impact femur fracture on 18 March 2020 :

NGWENDU, PHAPHAMA BETHELINA
DOB: 8/19/1977, Age: 42Y
Sex: F
64785021

GROOTE SCHUIJER HOSPITAL
CR 85
LOWER EXTREMITIES
Series: FEMUR AP- B
ACC: 55822778
C24-NX1

Series #: 1
Image #: 1/1
Acq Date: 3/18/2020
Acq Time: 14:25:19

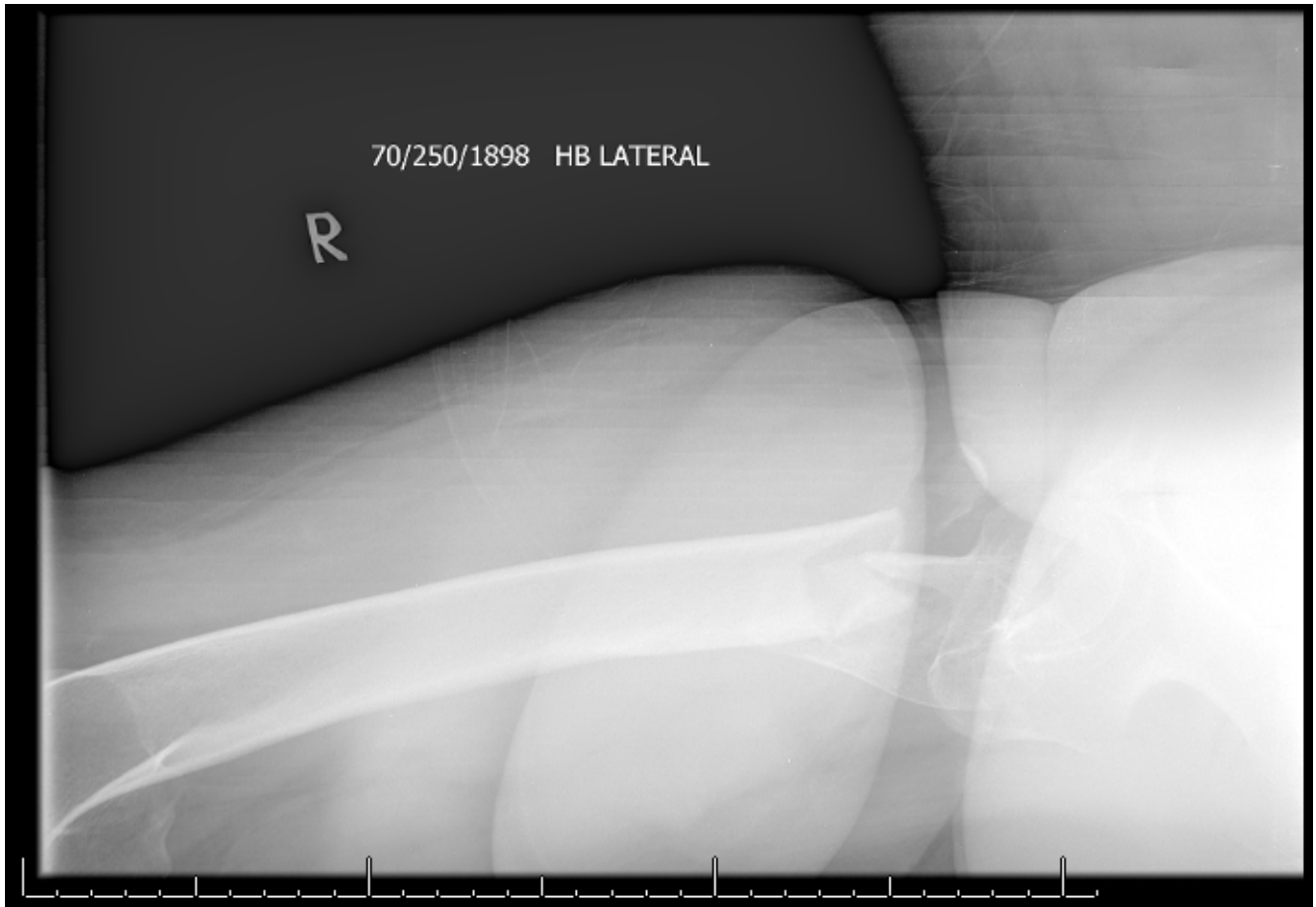
60/10/1213

R

wwwlwt: 15938/19875
Zoom: 14.4%

Tech: OCTOBER LOURENS





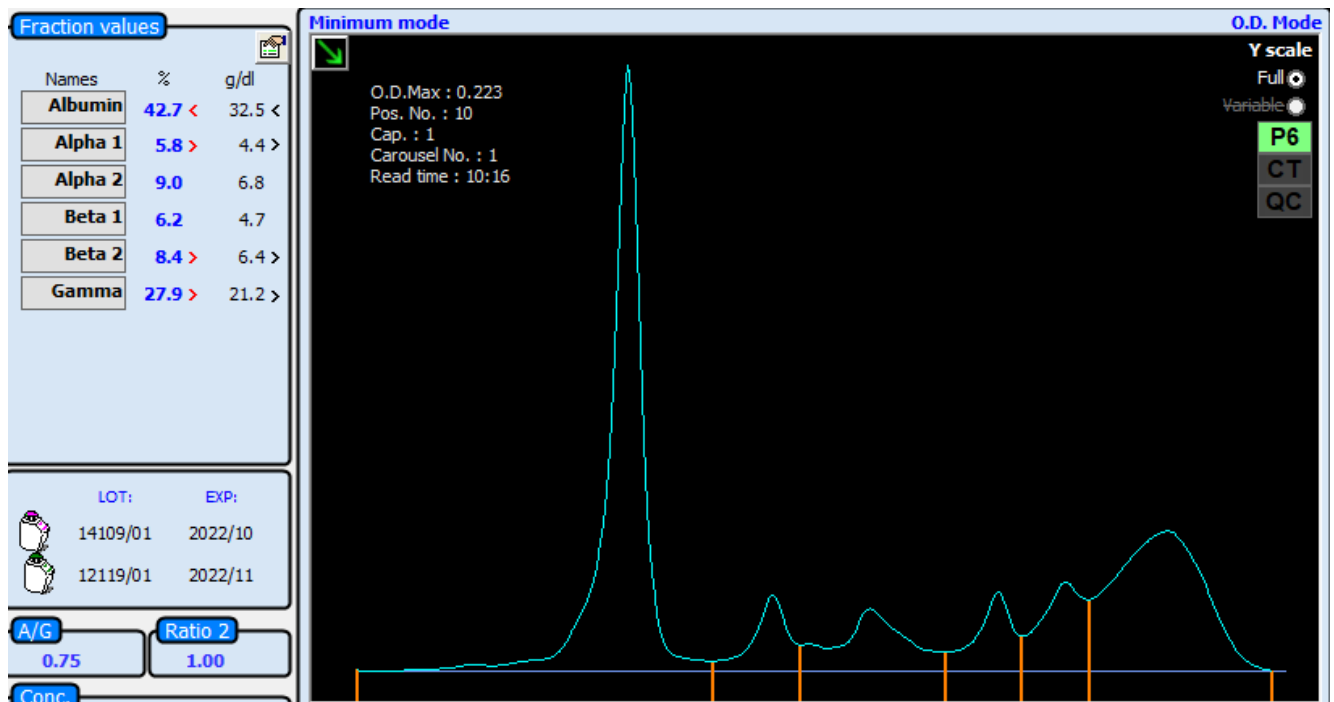
History

Patient is known with:

- previous deep venous thrombosis in 2018, on Warfarin therapy
- ?Epilepsy, patient is on carbamazepine, for which the Endocrinology specialists were of opinion that it may have been the cause of the low Vitamin D level.

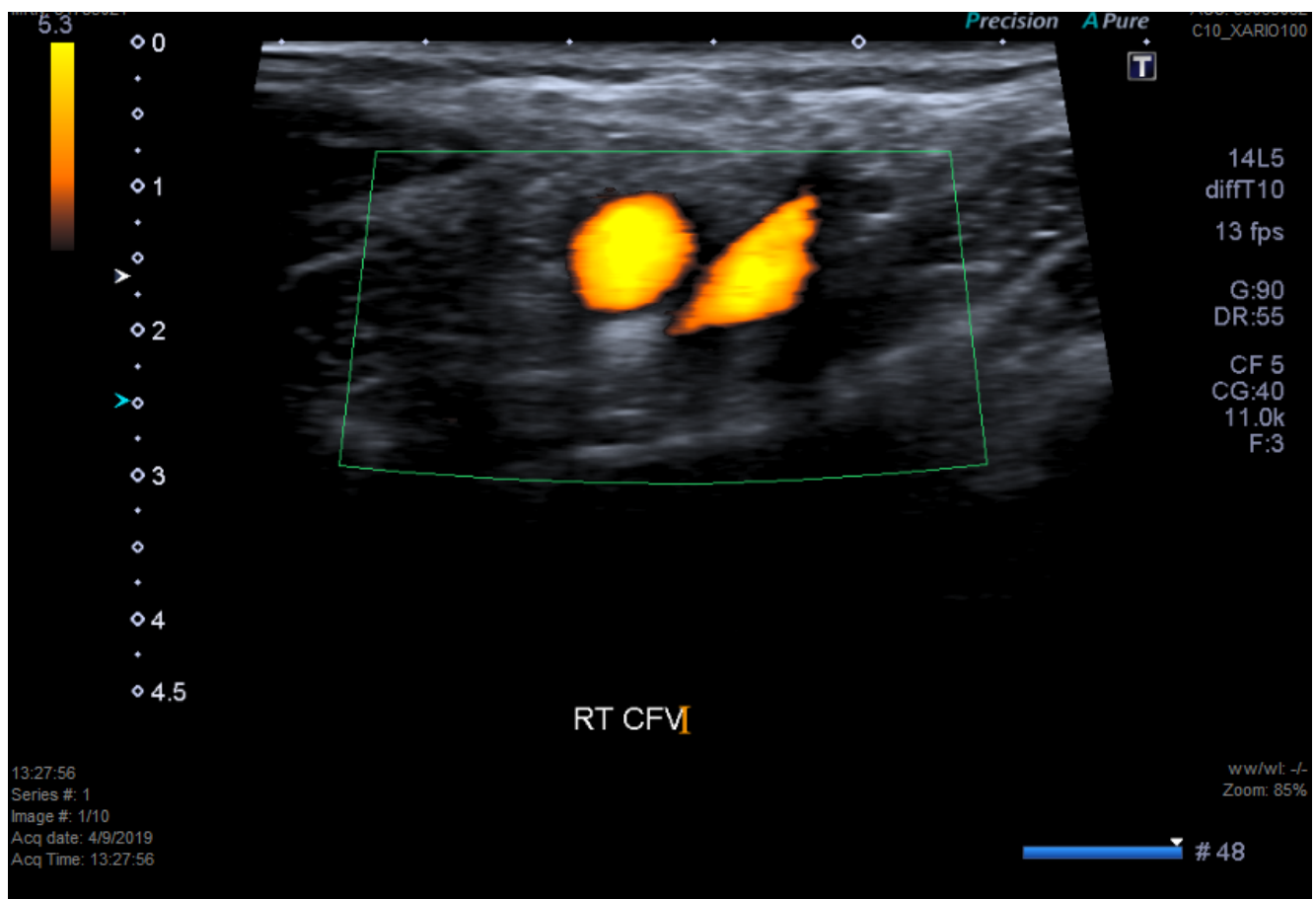
Examination

Laboratory Investigations



Serum protein electrophoresis pattern in keeping with an inflammatory process

Other Investigations



DVT in 2018

Final Diagnosis

Vitamin D deficiency likely due to carbamazepine therapy.

Take Home Message

I was not aware that patients on carbamazepine (or other enzyme inducing agents) have lower Vitamin D levels, and it became evident after a quick literature search that it was in fact the case, see the [abstract](#) of the article below, also see [another article](#) written by a colleague of mine, Jusine Cole, on the Vitamin D controversies.

[The Vitamin D cutoff conundrum](#)

Also, I have learned that although “total Vitamin D”, as the assay is named in our immunoassay package insert and on TrakCare LIS, has to do with the total portion with regards to protein binding (to Vitamin D binding protein) and not so much to the fact that calcitriol and calcidiol is measured.

It is however evident that, since the cross-reaction in the immuno-assay is quite pronounced with the various forms of Vitamin D, that total indeed, might be an accurate description. In reality, the assay is however called the Total 25-hydroxy Vitamin D.

Analytical specificity

The specificity was assessed at 50 % B₀ and the results are summarized in the following table:

Cross-reactant	Cross-reactivity (%)
25-hydroxyvitamin D ₃	100
25-hydroxyvitamin D ₂	92
24,25-dihydroxyvitamin D ₃	149
C3-epimer of 25-hydroxyvitamin D ₃	91
1,25-dihydroxyvitamin D ₃	not detectable
1,25-dihydroxyvitamin D ₂	not detectable
Vitamin D ₃	not detectable
Vitamin D ₂	not detectable

The Roche Package insert values for specificity for the Total 25-OH Vitamin D assay.

Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine.

Abstract

PURPOSE:

Evidence suggests that enzyme-inducing antiepileptic drugs (AEDs) may decrease serum 25-hydroxyvitamin D (25-OHD) levels and increase bone turnover. We sought to determine whether these are affected by treatment with carbamazepine (CBZ) or oxcarbazepine (OXC).

METHODS:

We measured serum levels of 25-OHD, parathyroid hormone (PTH), osteocalcin (OCLN), bone alkaline phosphatase (BAP), and urinary N-telopeptides of type I collagen cross-links (NTX) in normal controls (n=24) and in epilepsy patients taking CBZ (n=21) or OXC (n=24) in monotherapy. CBZ patients were

subsequently switched overnight to OXC monotherapy, and after 6 weeks, the tests were repeated.

RESULTS:

25-OHD levels were lower in each drug-treated group (OXC, 19.4+/-2.3 pg/ml; CBZ, 20.4+/-2.4) than in the controls (27.5+/-2.8) (ANOVA, $p=0.052$). This difference was significant for the OXC group ($p<0.05$). PTH, BAP, and NTX did not differ significantly among groups. OCLN levels were somewhat elevated in the OXC group (2.79+/-0.47 ng/ml) and more clearly and significantly elevated in the CBZ group (3.63+/-0.36) compared with controls (2.38+/- 0.41) ($p=0.053$). Because the data were very similar between OXC and CBZ groups, they were combined to increase statistical power. The combined drug-treatment group had significantly higher BAP ($p=0.02$) and lower 25-OHD ($p=0.015$) than did controls. The latter remained significant even after accounting for the confounding effects of age on 25-OHD levels ($p<0.05$). No significant differences were found after CBZ patients were switched to OXC.

CONCLUSIONS:

Epilepsy patients taking OXC or CBZ have significantly lower 25-OHD than do normal controls, with a pattern of changes in other bone biomarkers suggestive of secondary hyperparathyroidism. It may be prudent for patients taking CBZ or OXC to be prescribed 25-OHD replacement.

The Vitamin D cutoff

conundrum



Introduction

Vitamin D status is considered important for calcium balance and bone health as $1,25\text{ (OH)}_2$ vitamin D (calcitriol) promotes calcium absorption from the gut and has pleiotropic effects in bone. Vitamin D deficiency leads to hypocalcaemia and osteomalacia or rickets in adults and children respectively.

Vitamin D status was also brought under the spotlight owing to an apparent association with cardiovascular health and several other chronic disorders. These associations were noted in animal studies but the findings were not mirrored in humans. Vitamin D sufficiency or insufficiency is determined using quantitative analytical techniques, with results interpreted against statistically-determined cutoffs.

The Controversies

Controversies exist due to the analytical methods as well as the methods to determine these decision limits. The analytical methods available to quantify vitamin D include immunoassays and HPLC or LC-MS/MS methods. The majority of labs use immunoassays to measure 25(OH) vitamin D (calcidiol), and a smaller group also measure calcitriol by immunoassay. Calcidiol occurs at higher concentrations in the serum and, in most cases, it better reflects the vitamin status than calcitriol, as 1-alpha-hydroxylase activity is modulated according to calcitriol and calcium status.

However, immunoassays are non-specific regarding metabolites of vitamin D and therefore results of calcidiol and calcitriol measurement may not be accurate due to cross-reactivity. LC-MS/MS is a much more accurate methodology to measure both calcidiol and calcitriol as well as other metabolites of interest, such as 24,25(OH)₂ vitamin D. One controversial point is, therefore, whether or not calcidiol and calcitriol measurements by immunoassay are accurate.

The second controversy lies in the determination of the decision limits for vitamin D repletion, sufficiency and insufficiency. Currently, there are two major sets of decision limits to choose from. The first were determined and recommended by the Endocrine Society based on recommended daily allowances (RDA) for the vitamin. It is argued that the concept of the RDA is misinterpreted and the methods for setting the RDA not understood. These decision limits are high, and by these limits some 50% of most populations are diagnosed with vitamin D insufficiency. This is also dangerous, as replacement of vitamin D may lead to hypervitaminosis D, which is not benign and may in fact increase the risk of falls and fractures. Another consequence is the demand for testing vitamin D levels is very high, which is expensive for healthcare funders or individuals, with

questionable health benefits.

The other popular set of decision limits were determined based on the risk of falls and fractures (Institute of Medicine) – a more functional approach. The result of using these limits is that the majority of the population will fall into the vitamin D sufficient or replete groups, and only individuals at high risk will have their status checked and/or monitored and receive supplementation as necessary. This is a more cost- and clinically-effective approach, but is yet to be globally adopted.

	Vitamin D Status				
Institute of Medicine	25-OH D (ng/ml)		Endocrine Society	Treatment*	Maintenance†
Deficient	<12	<20	Deficient	50,000 IU/week for 6-8 weeks	600-2,000 IU/day
Insufficient	12-19				
Sufficient	20-29	20-29	Insufficient	≥400 IU/day	
	30-49	≥30	Sufficient		
High	>50				

The final point to be made is perhaps what drives the interest in vitamin D status, and it may be suggested that it is the reagents and pharmaceutical industry as they stand to gain from increased testing and demand for supplements.

Hypocalcemia

with

Hypomagnesemia

HOSP #		WARD	Internal Medicine ward
CONSULTANT	George vd Watt / Heleen Vreede / David Marais	DOB/AGE	58 y Male

Abnormal Result

Upon signing out blood results:

Calcium = 1.41 mmol/L – Critically low Calcium result

Magnesium = 0.37 mmol/L – Critically low Magnesium

Presenting Complaint

Loss of breath initially accompanied by weight loss.

Upon admission to the ward, patient was slightly delirious, but still able to walk and talk.

History

Patient with metastatic lung cancer and accompanying hypercalcemia, a week prior to the results as at present.

Doctor has given IV Bisphosphonate after the hypercalcemia was noted a week prior (Calcium = 4.23 mmol/L; Alb = 21 g/L; Corrected Ca = 4.61 mmol/L)

Examination

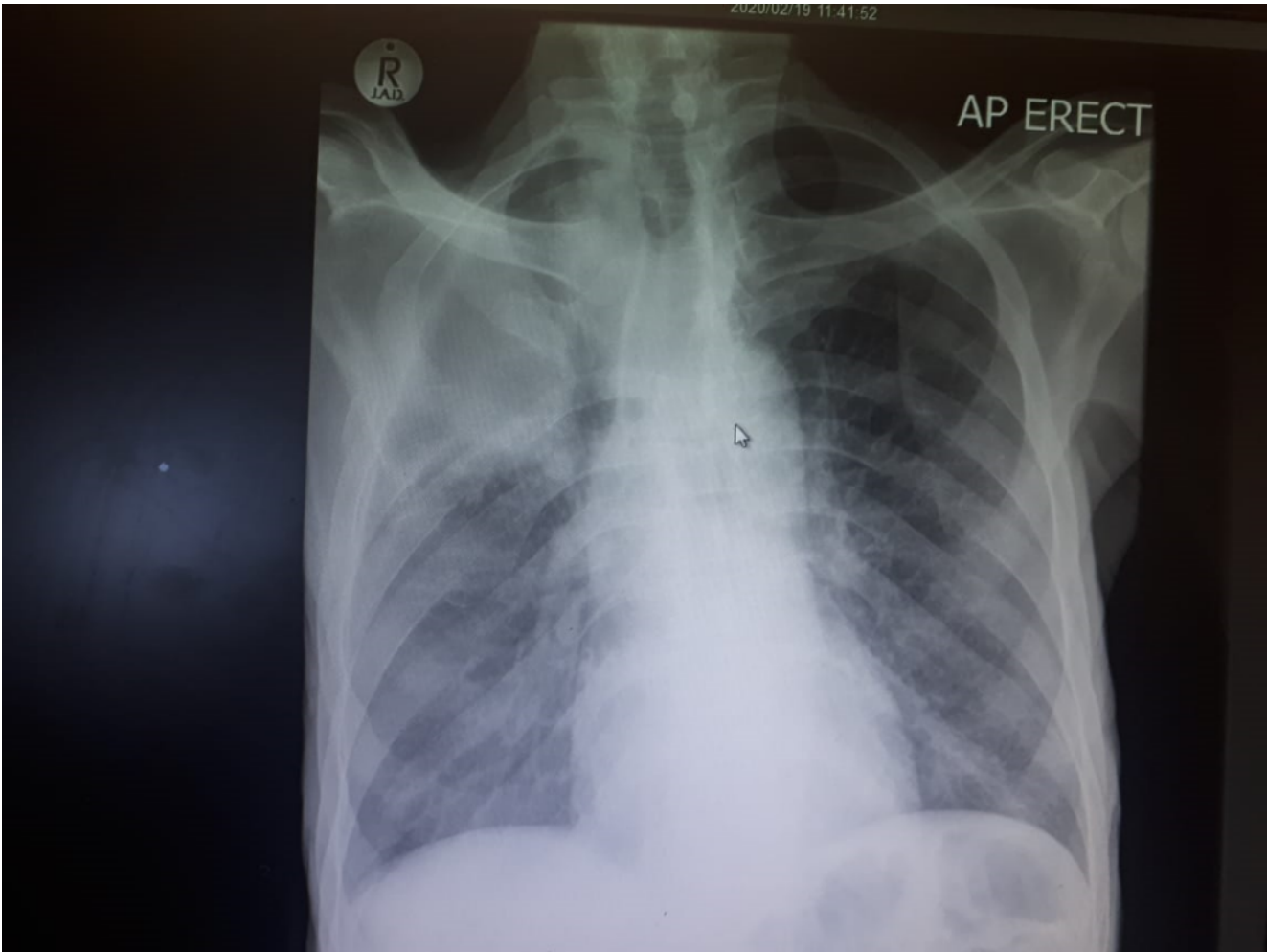
Extensive Crepitations over all the right lung fields.

Laboratory Investigations

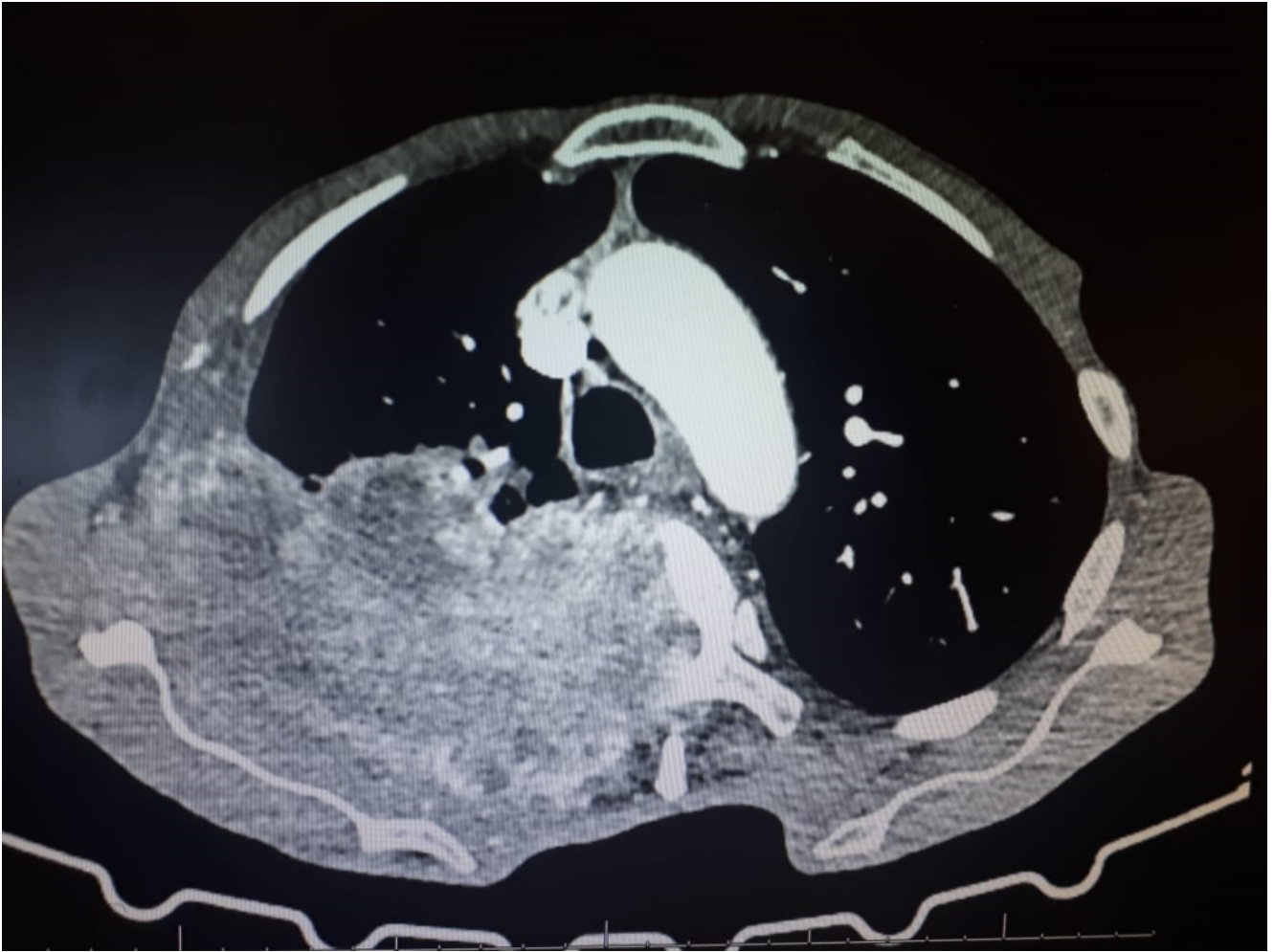
Test Set	Test Item	2020-02-26 11:49	2020-02-25 11:01	2020-02-24 19:20	2020-02-24 11:29	2020-02-23 11:48	2020-02-22 12:28	2020-02-21 16:50	2020-02-20 11:17	2020-02-18 17:07	2020-02-18 14:37	2020-02-17 23:44	2020-02-15 10:42	2020-02-15 3:34	2019-04-23 21:53
Test Set	Test Item														
NA	Na		132 L		133 L	133 L	135 L	138	δ- 139	δ+ 143	δ+ 139		132 L		
K	K		INVH		δ+ 3,4 L	δ- 2,4 L	δ+ 3,0 L	2,4 L	δ+ 2,8 L	δ- 2,1 L	δ- 3,2 L		4		
UREA	Urea		2,6		3,1	5,1	8,4 H	5,8	7,2 H	6,4	9,7 H		10,8 H	12,3 H	
CRT	Creat		44 L		51 L	63 L	82	94	δ+ 109 H	δ- 77	122 H		126 H	143 H	77
CA	Ca	δ- 1,41 L	1,78 L		δ- 1,76 L	δ- 2,02 L			δ+ 3,10 H	δ- 2,32	4,04 H		4,08 H	δ+ 4,23 H	
MG	Mg	0,37 L	δ- 0,38 L		δ+ 0,48 L	δ- 0,29 L							δ- 0,54 L	0,65	
PO4	Phos	δ- 0,51 L	δ+ 2,87 H		0,19 L	δ- 0,16 L							δ- 0,67 L	1,1	
ALB	Alb	25 L							25 L	CEGK	δ+ 28 L		20 L	21 L	
TBIL	tal bili													6	
CBIL	onj bili													2	
ALT	ALT													13	
AST	AST													23	
ALP	ALP													77	
GGT	GGT													29	
LD	LD													138	
PTH	PTH											0,6 L			
HVITDI	al Vit D											17,3			
HVITDI	Comment											VITD2			
HVITDI	HVITDIA											ST2			
HIVVL	VL (raw)													LDL	LDL
FBC	WCC				δ- 6,04									8,58	
FBC	RCC				δ- 2,80 L									3,17 L	
FBC	HB				δ- 7,9 L									9,4 L	
FBC	HCT				0,261 L									0,287 L	
FBC	MCV				93,2									99,4	

[Cumulative results ->Download](#)

Other Investigations



Chest X-Ray AP erect 19/02/2020



CT thorax

Final Diagnosis

Invasive lung CA with “hungry bones” after IV Zolendronic Acid

Vitamin D deficiency, preventing Calcium absorption after the Zolendronic acid started its action of inhibiting bone resorption.

Take Home Messages

CA causes hypercalcemia

Bisphosphonates inhibit bone resorption. Because 99.95% of Ca in the body resides in bone, the effect in serum (the remaining 0.05% of total body Ca) can be significant.

All bisphosphonate drugs share a common phosphorus-carbon-phosphorus “backbone”:



They differ in the R-groups as above. It binds to calcium hydroxyapatite in bone.

Of the dose infused / absorbed, 50% is excreted unchanged by the kidney, the rest binds to bone tissue, where its elimination half life can apparently be up to 10 years! (UW

Courses

Web

Server-

<https://courses.washington.edu/bonephys/opbis.html>)

Because a bisphosphonate group mimics the structure of pyrophosphate, it can inhibit activation of enzymes that utilize pyrophosphate.



Magnesium follows Calcium levels, but Mg deficiency itself can also cause hypocalcemia.