The Vitamin D conundrum

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

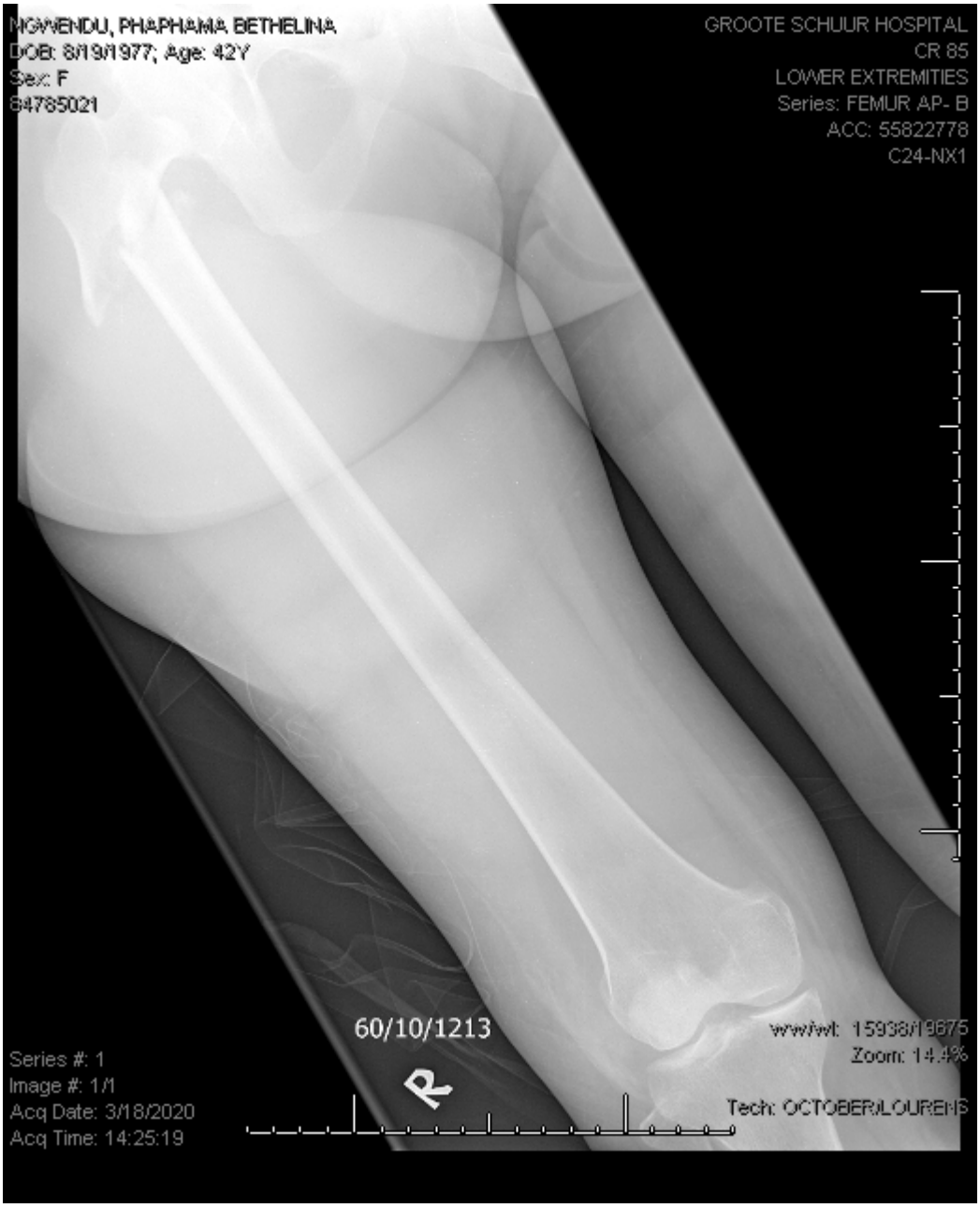
Abnormal Result

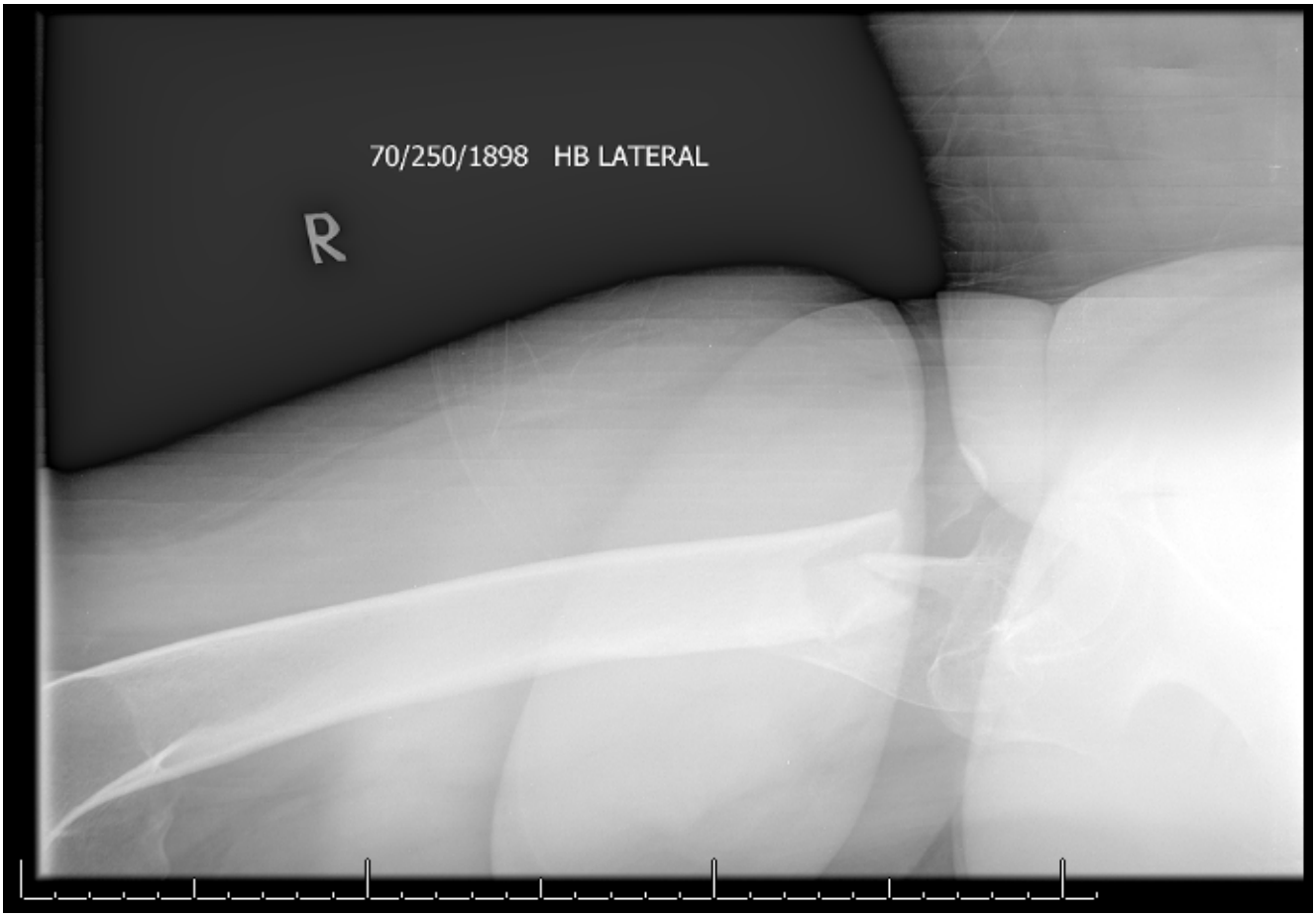
Total Vitamin D of 27.1 nmol/L on 18 March 2020.

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
84785021
GROOTE SCHUUR HOSPITAL
CR 85
LOWER EXTREMITIES
Series: FEMUR AP- B
ACC: 55822778
C24-NX1
60/10/1213
R
Series #: 1
Image #: 1/1
Acq Date: 3/18/2020
Acq Time: 14:25:19
ww/wl: 15938/19875
Zoom: 14.4%
Tech: OCTOBER/LOUREN



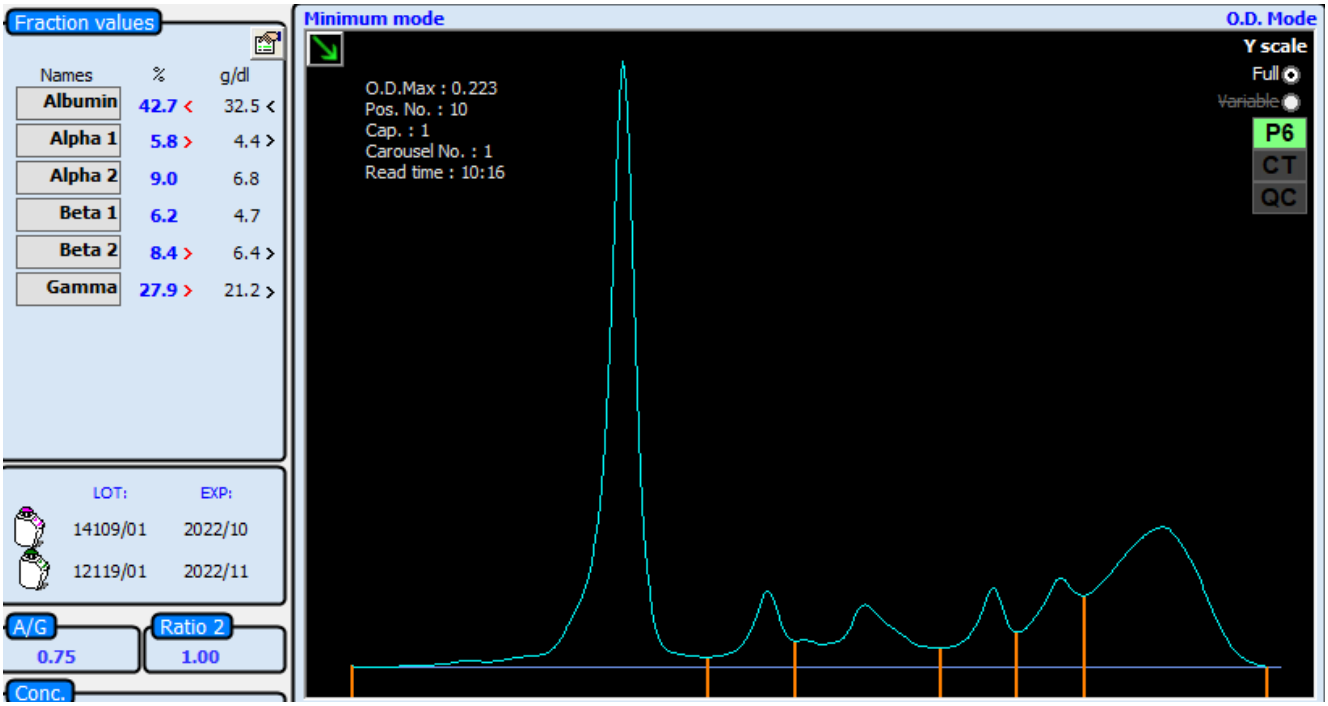
History

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.

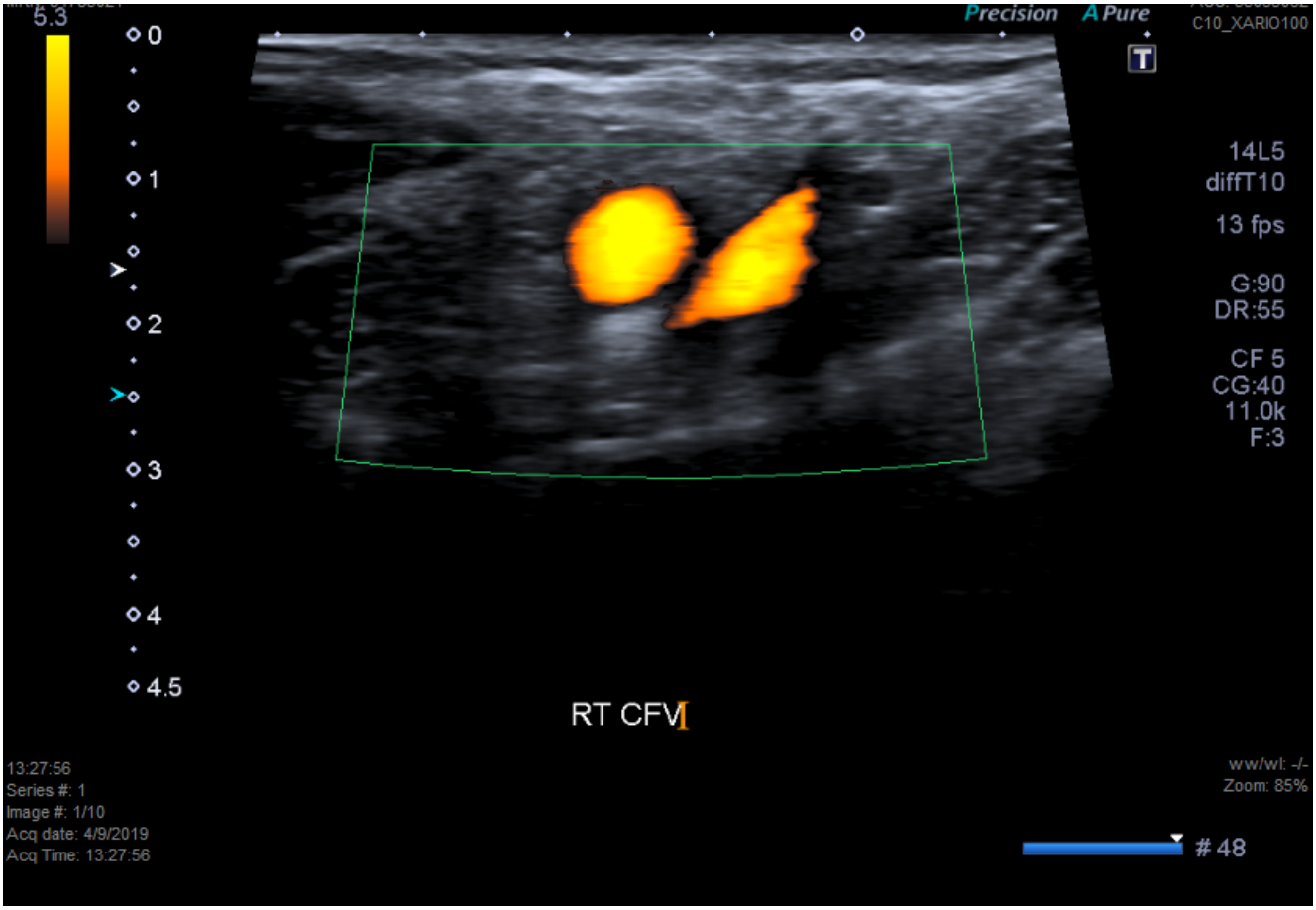
Examination

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 % B_0 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 (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.

<table>
<tr><td></td><td colspan="2">Vitamin D Status</td><td></td><td></td><td></td></tr>
<tr><td>Institute of Medicine</td><td colspan="2">25-OH D (ng/ml)</td><td>Endocrine Society</td><td>Treatment*</td><td>Maintenance†</td></tr>
<tr><td>Deficient</td><td><12</td><td rowspan="2"><20</td><td rowspan="2">Deficient</td><td rowspan="2">50,000 IU/week for 6-8 weeks</td><td rowspan="2">600-2,000 IU/day</td></tr>
<tr><td>Insufficient</td><td>12-19</td></tr>
<tr><td rowspan="3">Sufficient</td><td>20-29</td><td>20-29</td><td>Insufficient</td><td colspan="2" rowspan="3">≥400 IU/day</td></tr>
<tr><td>30-49</td><td rowspan="2">≥30</td><td rowspan="2">Sufficient</td></tr>
<tr><td>High</td><td>>50</td></tr>
</table>

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.