

Vitamin D deficiency has no impact on PSA reference ranges in a general university hospital – a retrospective analysis

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ABSTRACT

Background

Vitamin D deficiency has been linked to a higher risk of prostate cancer. We tested the hypothesis that vitamin D levels would have an impact on prostate specific antigen (PSA) levels.

Methods

From our laboratory database we selected 5136 male patients with simultaneously determined vitamin D and PSA levels. Subgroups of several age cohorts with different vitamin D levels were created and PSA 95 percentile values were assessed. The independent effect of vitamin D levels and age on PSA levels was determined with logistic regression.

Results

PSA levels increased with age, while no difference was identified in PSA levels in different vitamin D subgroups.

Conclusion

Vitamin D levels do not have an effect on PSA. Hence, there is no need to adjust PSA reference ranges and threshold values to vitamin D levels during the process of decision making



INTRODUCTION

Epidemiological observations and, quite recently, an interventional trial indicated the possible role of vitamin D3 and its supplementation in the prevention of prostate cancer. [1] The results of the recent VITAL trial support that vitamin D3 supplementation in a dose of 2000 IU/day decrease the mortality from prostate cancer by up to 12 percent. [2] Large doses of daily vitamin D3 supplementation and appropriate levels of the active vitamin D inhibit the transition of early, low-risk prostate cancer to more aggressive forms.[3,4] The benefits of vitamin D in the therapy of advanced prostate cancer, however, are less conclusive. [5]

The mechanism of protection of prostate health provided by vitamin D is extensively studied. Different effects of vitamin D on prostate cells were identified. Vitamin D receptor as a nuclear receptor has a significant impact on gene regulation implicated in prostate cell differentiation and metabolism and is generally acknowledged as an antitumor agent. [6, 7] More recent data indicate that non-genomic effects, particularly those affecting mitochondrial respiration may also play a role. [8] Another study revealed that appropriate levels the active vitamin D metabolite inhibits the intracrine conversion of dehydroepiandrosterone to prostate growth-stimulating androgens such as testosterone and dihydrotestosterone. [9]

Prostate specific antigen (PSA) has been widely used as a screening test for detection of prostate cancer. Albeit the ordering of PSA is not

recommended routinely, many clinicians still adhere to request this test even for symptom-free men. In general, those patients exhibiting PSA values over a pre-specified threshold are referred to urologists often with suspected prostate cancer and considered as candidates for more invasive interventions.

This approach is inherent with the risk of unnecessary investigations of patients with false positive PSA values. False positive rate depends largely on threshold values used. Commonly used threshold value is 4 µg/L, but it is not routinely adjusted to extra-prostate factors having an impact on PSA. Some of these extra-prostate factors as age are widely known, while others such as thyroid function, daily or seasonal variations are identified more recently. [10,11]

As PSA is widely considered as a surrogate marker for prostate pathology, we hypothesized that low vitamin D levels is associated with higher PSA at population level. In our analysis we tested whether low vitamin D levels may have an independent impact on PSA levels and reference ranges in different age cohorts.

METHODS

The Department of Laboratory Medicine offers PSA and vitamin D determination to 44 University Hospitals of Semmelweis University, Budapest, Hungary. From Laboratory Informatics System we retrieved records generated since January 1, 2011 that included the following fields: anonymized patient identification number; gender; age; date of measurement; the name of the measured parameter; test result; reference range and unit; and instrument used for testing.

Out of the collected ≈200 million records we selected those that fulfilled the following criteria: (1) male gender and (2) we determined vitamin D levels or PSA levels. Vitamin D and PSA levels were measured by CE IVD qualified, commercially available immunoassays. In order to

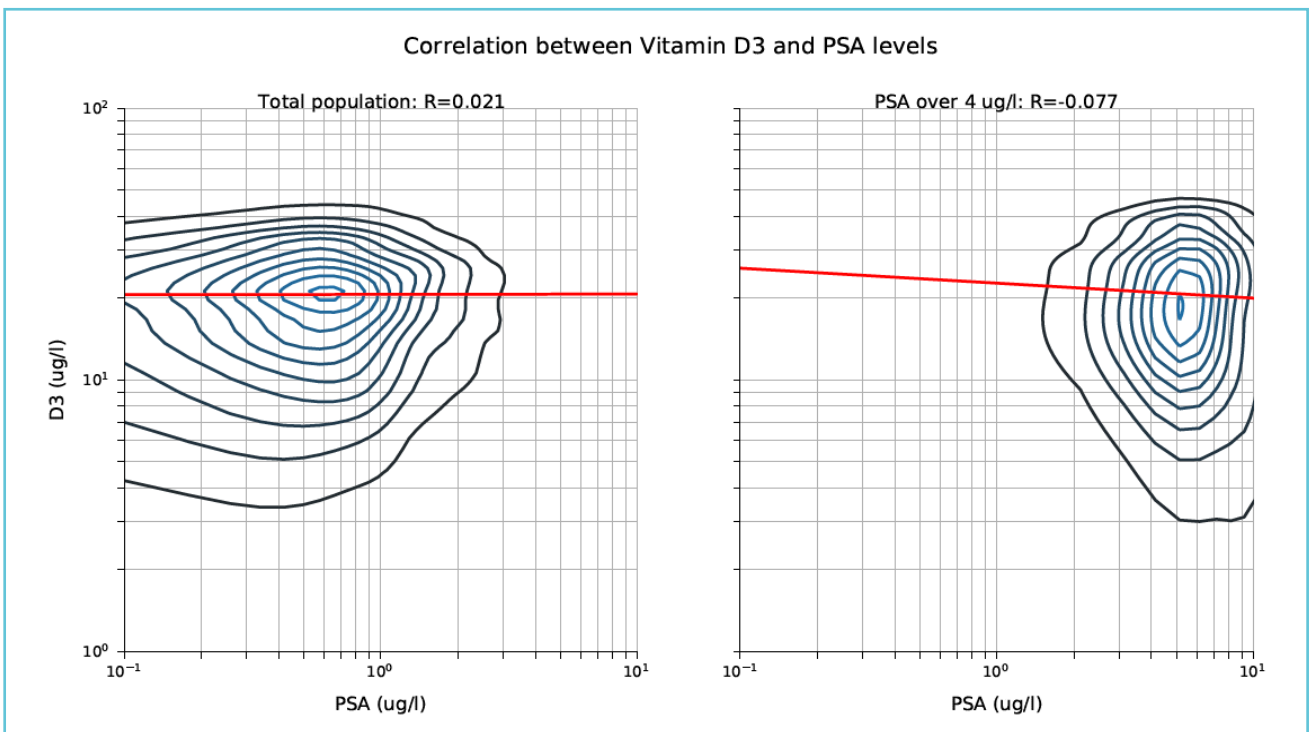
exclude patients with severe prostate pathology we arbitrarily excluded records with PSA levels above 20 $\mu\text{g/L}$ from further analysis. Then we selected those patients having both PSA AND vitamin-D level measurements within 30 days. From the created database we selected those data pairs for an individual patient [n = 5136] that were measured for the first time in our database.

We generated subgroups and cohorts according to vitamin D levels and age and calculated the 95

percentile values as the upper level of reference range. We also assessed the rate of subjects with elevated PSA ($>4 \mu\text{g/L}$).

In addition, the independent effect of vitamin D levels and age on PSA levels was determined with logistic regression analysis of the logarithmic data. (Statistical analysis was performed with R software package.) The data analysis was approved by an Independent Ethical Committee of the University. We also investigated the direct correlation between vitamin D3 and PSA levels.

Figure 1 Bivariate kernel density estimates of PSA and vitamin D3 values measured in our laboratory between 10/2007 and 06/2018



Closed lines represent coordinates with equal density of data in the two-dimensional space, smoothed by a Gaussian function.

Pearson's correlation coefficient (R) is calculated after logarithmic transformation of both PSA and vitamin D3 levels in order to achieve a close-to-normal distribution in individual dimensions. Linear regression line for the logarithm of data points is shown in red.

Two-dimensional distribution and correlation was calculated for both the total patient population (left side) and only for patients with PSA above 4 $\mu\text{g/l}$ (right side).

Due to the characteristics of the PSA test, any value measured to be below 0.1 $\mu\text{g/l}$ is reported here as 0.1 $\mu\text{g/l}$. This bias is, however, corrected by kernel density estimation.

Pearson's correlation coefficients found here were close to 0 suggesting the absence of linear relationship between PSA and vitamin D3 levels.

Table 1 Reference ranges of PSA levels in an ageing population with different vitamin D serum levels

Distribution of patients (total number: 5136) according to age and vitamin D levels

Age (years)	<50	50 – 59	60 – 69	at least 70
Vitamin D (µg/L)				
<15	280	226	309	327
15-30	806	677	755	629
30<	351	229	300	247

PSA 95 percentile values (µg/L) in different age cohorts with different vitamin D levels

Age (years)	<50	50 – 59	60 – 69	at least 70
Vitamin D (µg/L)				
<15	2.0	3.4	7.7	11.0
15-30	2.1	3.8	7.0	9.4
30<	2.4	4.7	8.2	8.7

Per cent rate of patients with PSA >4 µg/L

Age (years)	<50	50 – 59	60 – 69	at least 70
Vitamin D (µg/L)				
<15	1.0%	3.9%	14.9%	22.3%
15-30	0.7%	5.3%	12.4%	18.2%
30<	1.4%	6.5%	16.3%	23.4%

Pearson’s correlation coefficient (R) was calculated after logarithmic transformation of both PSA and vitamin D3 levels in order to achieve a close-to-normal distribution in individual dimensions. Two-dimensional distribution and correlation was calculated for both the total

patient population and solely for patients with PSA above 4 µg/l (Figure 1). Due to the characteristics of the PSA test, any value measured to be below 0.1 ug/l is reported here as 0.1 ug/l. This bias is, however, corrected by kernel density estimation.

RESULTS

The majority of patients (55.8 and 22.2 percent) had moderate or severe vitamin D deficiency hallmarked by 15 – 30 µg/L and <15 µg/L vitamin D levels, respectively. While PSA levels increased with age, no difference in PSA levels was identified between patients with different vitamin D levels (see Table 1).

Our logistic regression analysis indicated a significant association between age (estimate: 0.010; SE: 0.0027, p=0.003), while no impact of vitamin D on PSA levels was found. In fact, Pearson's correlation coefficients found here were close to 0 suggesting that there was no linear relationship between PSA and vitamin D3 levels.

DISCUSSION

Several reports suggested an inverse relationship between vitamin D levels and the risk and aggressiveness of prostate cancer [1-3]. Therefore, it was reasonable to postulate that the presumed effect of vitamin D on prostate would be reflected in PSA, a surrogate marker of prostate pathology. However, the results of our analysis involving 5136 data pairs of vitamin D and PSA levels of general hospital patients, does not support this hypothesis.

These findings are in line with those of several smaller studies that searched for an association between vitamin D levels and PSA levels.

A prospective study enrolling 105 healthy men without any basic alteration of PSA documented no change in PSA levels upon vitamin D administration and increase in vitamin D blood levels. [12] In 71 patients on peritoneal dialysis no association between vitamin D and PSA was identified. [13] Another study enrolling 1705 subjects found no direct relationship between PSA and vitamin D levels in patients without prostate cancer. [14]

The novelty of our study that we performed our analysis on a larger group (more than 5000) unselected patients treated at the University. We were not aware of diagnosis and treatment. We are, however, convinced that this limitation does not prevent to draw the conclusion that vitamin D levels have due to the large number of data, heterogeneity of referring departments and the exclusion of patients with high PSA levels.

Our finding has two major implications for interested readers. First, it raises concern about the contribution of vitamin D to those prostate pathologies that are clearly indicated by slightly or moderately elevated PSA levels. Second, it reinforces for clinicians that they should not adjust PSA reference ranges and threshold values to vitamin D levels during the process of decision making.



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