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RESEARCH

Vitamin D [25(OH)D] and 1,25(OH)$_2$D serum concentrations in patients tested at the Charlotte Maxeke Johannesburg Academic Hospital

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Introduction: There has been a significant increase in vitamin D [25(OH)D] testing in recent years.
Aims: To describe the number of tests, concentrations for 25(OH)D and 1,25(OH)$_2$D in adults (≥ 18 years), characteristics of those tested and to determine the 25(OH)D concentration at which parathyroid hormone increases (PTH threshold).
Methods: Data were extracted for 25(OH)D and 1,25(OH)$_2$D tests, from the National Health Laboratory Services data warehouse for Charlotte Maxeke Johannesburg Academic Hospital from 2015 to 2017. Results were categorised by age, sex and race. Vitamin D status was described using National Academy of Medicine guidelines. The PTH threshold was determined by LOWESS plots.
Results: 25(OH)D and 1,25(OH)$_2$D tests increased, with no change in median concentrations over time. Black Africans (6.7%) had the highest prevalence of Vitamin D deficiency (VDD). Males had significantly lower 25(OH)D values ($p < 0.001$) and a higher proportion of VDD ($p = 0.009$). Younger patients (< 30 years; 7.9%) and elderly (> 74 years; 10.5%) black Africans had highest prevalence of VDD. The PTH threshold differed by race group.
Conclusions: Clear testing guidelines are needed to curb test overutilisation. Further work is required to understand the appropriate cut-off levels to define VDD in our populations.

Keywords: age, black Africans, South Africa, trends, Vitamin D deficiency

Introduction

There has been increasing interest in the medical community in the role of vitamin D [25(OH)D] in bone and cardiovascular health, cancers, autoimmune diseases and diabetes mellitus, as well as infectious diseases such as tuberculosis.[1,2] The possible 25(OH)D health benefits with regard to these diseases may explain the marked increase in 25(OH)D analysis noted in laboratories worldwide over the last decade.[3,4]

The cut-off values used to define vitamin D deficiency (VDD), insufficiency and sufficiency remain controversial. Currently there are two main diagnostic guidelines issued by the United States Endocrine Society and the National Academy of Medicine (NAM), formerly known as the Institute of Medicine (IOM).[1,5,6] The latter guidelines use the following cut-offs to define vitamin D deficiency, insufficiency and sufficiency: <30 nmol/l, 30–50 nmol/l and > 50 nmol/l[1,5], respectively. These are different from the cut-off levels as defined by the United States Endocrine Society.[1,6] Using the NAM cut-offs, a recent systematic review and meta-analysis of VDD in Africa noted that one in five people have a 25(OH)D level < 30 nmol/l despite year-long sunlight exposure.[7] The overall pooled prevalence was reported as 18.46% (95% CI 10.66–27.78), with South Africa and northern African countries reported to have the lowest vitamin D levels.[7]

The parathyroid hormone (PTH) threshold, a plateau point for 25(OH)D below which there is a rise in PTH (secondary hyperparathyroidism), has been considered an indication of VDD.[8] These cut-off levels specifically pertain to bone health, as levels in other diseases for deficiency or sufficiency have not been well defined.[1,6] There are limited data on the appropriate cut-off levels to use in Africans. A systematic literature review in 2006 of studies analysing the association between PTH and 25(OH)D levels revealed a putative threshold between 25 and 122 nmol/l[8], while a study carried out in African American and white women showed different cut-offs for both races with a threshold of 37 nmol/l in black women and 59 nmol/l in white women.[8] This threshold appears to be dependent on race, age, body composition, renal function and geographical location.[5,8]

Currently, 25(OH)D (comprising D_2 and D_3) is used to assess vitamin D related disorders and the body's vitamin D stores.[1,6] Analysis of 1,25(OH)$_2$D is required only in limited circumstances, which include vitamin D-dependent rickets type 1, autosomal-dominant hypophosphataemic rickets and X-linked hypophosphataemic rickets (mutations that result in elevated levels of FGF-23).[6] The monitoring of 1,25(OH)$_2$D in patients with chronic kidney disease (CKD) is not currently advocated by the 2017 Kidney Disease Improving Global Outcomes (KDIGO) guidelines on bone mineral disorders.[9,10] The testing of 25(OH)D is costly and the current consensus among experts is that testing should only be performed on those at increased risk of VDD.[3,6,11]

The objectives of the current study were to (i) describe test numbers for both 25(OH)D and 1,25(OH)$_2$D from our laboratory over a three-year period, (ii) to describe the vitamin D profiles for 25(OH)D according to NAM guidelines by age, sex and race, (iii) to determine the PTH threshold for VDD by race for those with normal renal status and (iv) to assess the percentage of 25(OH)D and 1,25(OH)$_2$D requests in patients with CKD.

Methods

Study design and setting

This was a retrospective study using laboratory data extracted from the corporate data warehouse (CDW) of the National Health Laboratory Services (NHLS) for the period 1 January 2015 to 31 December 2017. The extracted data included all total 25(OH)D, 25(OH)D$_2$, 25(OH)D$_3$ and 1,25(OH)$_2$D results carried out in the NHLS, Department of Chemical Pathology laboratory based at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). Our laboratory received vitamin D requests from across the South African public sector. This study was approved by the Ethics Committee of the University of Witwatersrand (M180808).

Study population selection

The sample population was adults (≥ 18 years), who had either 25(OH)D and/or 1,25(OH)$_2$D tests done during the study period. Additionally, the accompanying results (total serum calcium, inorganic phosphate, creatinine, estimated glomerular filtration rate (eGFR), alkaline phosphatase (ALP) and PTH) taken within a week of the vitamin D result were included to obtain a complete profile.

Race was categorised into five groups: white, black African, Indian, multiracial and unknown. The 'unknown' category was used when race could not be assigned and is described in the supplementary material. The 25(OH)D results were separated into 25(OH)D$_2$ and 25(OH)D$_3$ by race and subdivided by sex. The population was categorised according to the NAM criteria.[1,5]

To determine test numbers, we excluded samples from patients < 18 years and quality assurance (QA) samples. Repeat tests, whether 25(OH)D or 1,25(OH)$_2$D, done from the same patient during the study period, were identified by means of a unique patient identifier. The unique patient identifier, implemented at the CDW, uses a probabilistic matching record linkage algorithm. The number of samples over the three-year period was reported, after which repeat tests were excluded from the detailed descriptive analysis to determine the distribution of 25(OH)D concentrations, patient characteristics and season of testing.

Laboratory methods

25(OH)D was measured by high-performance liquid chromatography (Shimadzu Corporation, Long Beach, CA, USA) with separation into 25(OH)D$_2$ and 25(OH)D$_3$, and 1,25(OH)$_2$D was measured by competitive radioimmunoassay (Immunodiagnostics Systems Holdings PLC, Tyne & Wear, UK). The other methods used were immunoassay (PTH), colorimetric (serum total calcium, serum inorganic phosphate, ALP) and enzymatic (creatinine) assays performed on the Roche Cobas 8100 (Roche Diagnostics Ltd, Mannheim, Germany). The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[12] We defined CKD as a consistent eGFR < 60 ml/min/1.73^2 for more than three consecutive months.

Statistical analysis

Data analysis was done using Statistical Analysis Software (SAS) 9.4 (SAS Institute, Cary, NC, USA) and Microsoft Excel 2016 (Microsoft Corp, Redmond, CA, USA). The mean with standard deviation (SD) was reported for normally distributed data and the median with interquartile ranges for skewed data. Descriptive data analysis was used to describe the 25(OH)D profiles. We used ANOVA to compare continuous parametric data by race, Kruskal Wallis for non-parametric continuous data and a chi-square test for categorical data, with statistical significance set at $p < 0.05$.

As race group was specified for very few patients, we used the hot deck imputation algorithm to impute missing values using well-populated cancer registry data with patient-reported race group data.[13] The National Cancer Registry (NCR) data was used to construct the imputation reference panel (approximately 1.2 million values).[14] Locally weighted scatter plot smoothing (LOWESS) was used to determine the relationship between 25(OH)D and PTH across race groups in patients with normal renal status.

Results

Over the three-year period, 15 407 tests were identified of which 3 283 were excluded, giving a final number of 12 124 tests. After exclusion of repeat testing, a cohort of 10 008 patients was used for the descriptive data analysis as shown in Figure 1. The 25(OH)D and 1,25(OH)$_2$D tests comprised 7 383 and 2 600 patients respectively, with 25 patients having both tests.

We noted an increase in test numbers across the three-year period as indicated in Figure 2A. The 25(OH)D test volumes increased from 1 982 in 2015 to 2 786 in 2017. This was a 53% and 18% increase between 2015–2016 and 2016–2017, respectively. The increase in 1,25(OH)$_2$D test volumes shown represented a 22% and 13% increase between 2015–2016 and 2016–2017, respectively. There was no significant change in median 25(OH)D and 1,25(OH)$_2$D levels over this period. The greatest increases in testing were seen in black African males and females (Figure 2B). This represented a 75.70% increase in testing of black African males and an 88.10% increase in black African females over the three-year period. The majority of tests were requested from the Gauteng (73.10%), KwaZulu-Natal (10.70%) and the Eastern Cape (6.30%) provinces (data not shown).

Within the total cohort, 3 884 (45.40%) were black African, 2 387 (27.90%) white, 875 (10.20%) Indian, 765 (8.90%) multiracial and 638 (7.60%) of unknown ethnicity (see Supplementary Table 1). Overall, black Africans were significantly younger than all other racial groups ($p < 0.0001$, 50.65 ± 16.88 years). Black Africans had the lowest levels of 25(OH)D (69.00 (47.20–95.20) nmol/l), which was significantly lower when compared with the other racial groups ($p < 0.0001$). Additionally, black Africans also had the lowest D$_2$ levels (7.00 (7.00–34.41) nmol/l) (Table 1).

In the total cohort by race and sex, the majority of patients were female (73.50%). The male mean age was lower as compared with females for all racial groups ($p < 0.001$). Black African and multiracial males were younger than white and Indian males (46.90 ± 15.70 and 50.90 ± 16.80 vs. 56.20 ± 17.00 and 53.20 ± 15.90 years), respectively (Table II).

The total 25(OH)D levels for males across all racial groups were found to be lower than females ($p < 0.05$), with the lowest values in Indian (63.70 (44.10–86.10) nmol/l) followed by black African (69.90 (48.40–96.80) nmol/l) males. Females had higher 25(OH)D$_2$ levels when compared with males across all racial groups ($p < 0.0001$), and males had higher 25(OH)D$_3$ compared with females across all racial groups ($p < 0.0005$) as seen in Table 2. There was no difference by race or age category in median 25(OH)D$_2$ levels (data not shown).

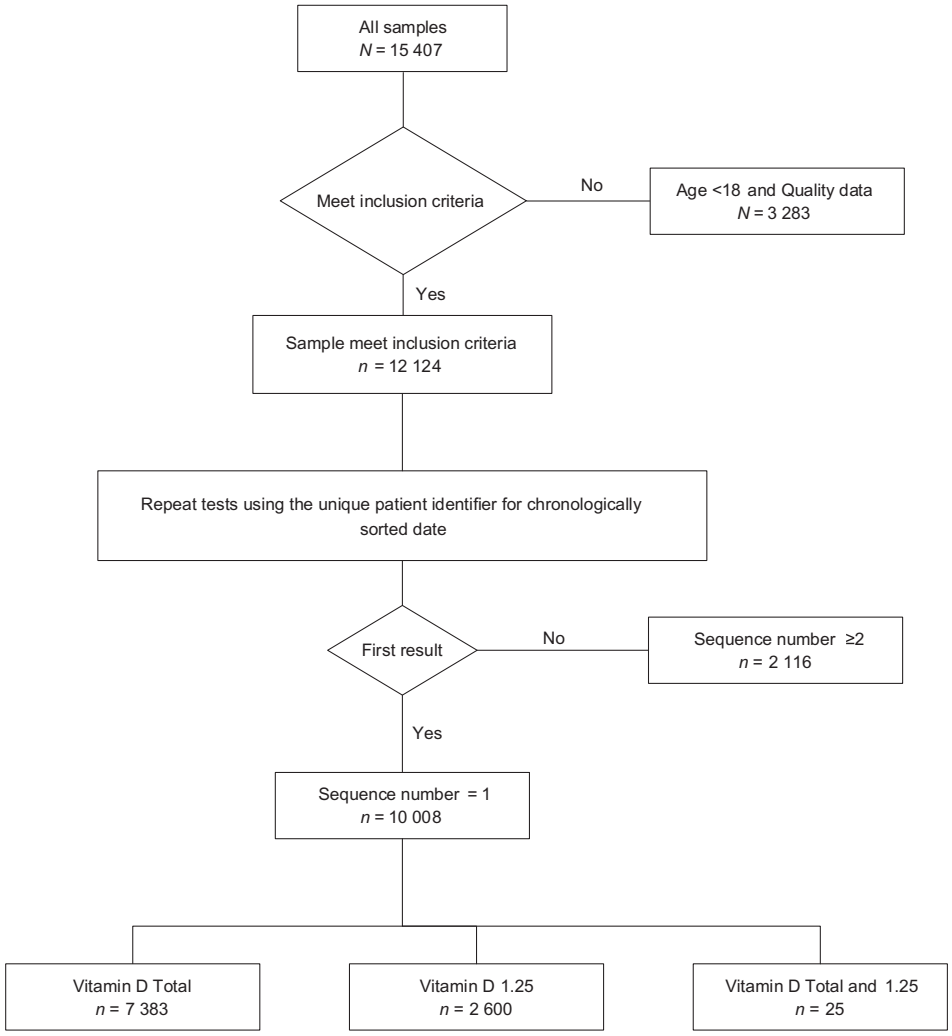

Figure 1: Study population selection. Exclusion criteria applied to reach the final 25(OH)D and 1,25(OH)$_2$D results used for data analysis.

Analysis of 1,25(OH)$_2$D levels showed that median concentrations were all within the laboratory-defined reference range of 43–168 pmol/l, with no statistically significant differences between racial groups. Black African males had the highest median PTH (11.2 pmol/l). Additionally, black African females and males had the highest proportion (40.00% and 23.10%) of CKD as compared with other racial groups (see Table 2).

The majority of 25(OH)D results were categorised as sufficient (Table 3, Figure 3), with the highest proportion of sufficiency in white (83.70%) and multiracial (80.10%) patients. The overall prevalence of VDD was 5.50%, with proportionately more black African and Indian patients deficient (6.70% and 6.60%) and insufficient (20.40% and 18.30%) ($p < 0.001$). Vitamin D insufficient and deficient patients were younger than those that were sufficient ($p < 0.05$ and $p = 0.0001$, respectively). More males as compared with females ($p < 0.009$) were found to be deficient (6.10% vs. 5.20%) and insufficient (19.40% vs. 16.90%). By age category, the highest proportion of VDD (7.90%) and insufficiency (20.60%) was seen in the < 30 years category (see Table 3). In patients with CKD, the prevalence of VDD was 5.80% across all racial groups.

The median serum calcium level was found to be significantly lower in the deficient group (2.06 [1.26–2.29)] mmol/l) as compared with 2.33 (1.86–2.44) mmol/l in the sufficient group ($p = 0.001$). Median inorganic phosphate and ALP were within the normal reference ranges across all three categories. Median PTH levels were elevated across all categories (reference range of 1.6–6.0 pmol/l), with a significantly higher level found in the deficient category (11.5 (1.3–32.2) pmol/l) as compared with the sufficient category ($p = 0.0001$) (see Table 3).

Further analysis by race and age (Figure 3) showed that VDD varied across racial groups. Among those over the age of 74, the prevalence of VDD was highest in black African patients (10.50%).

The highest proportion of VDD patients were from the Free State (9.1%), Limpopo (6.3%) and the Eastern Cape (6.2%) provinces. Provinces with the least VDD were North West (1.2%), Mpumalanga (4.9%) and the Western Cape (3.7%) (data not shown). We looked at seasonal variation in VDD and noted that it was highest in the winter (7.78%), and lowest in late autumn (7.78% vs. 3.43%, $p = 0.0001$) (data not shown).

Creatinine results were available for 1 588 patients, of whom 844 (53.15%) had CKD. In the CKD group, 822 (97.39%) and 22 (2.61%) of requests were identified as 25(OH)D and 1,25(OH)$_2$D, respectively. The prevalence of VDD was 6.50% and 7.52%, in males and females with CKD respectively (Supplementary Table 2).

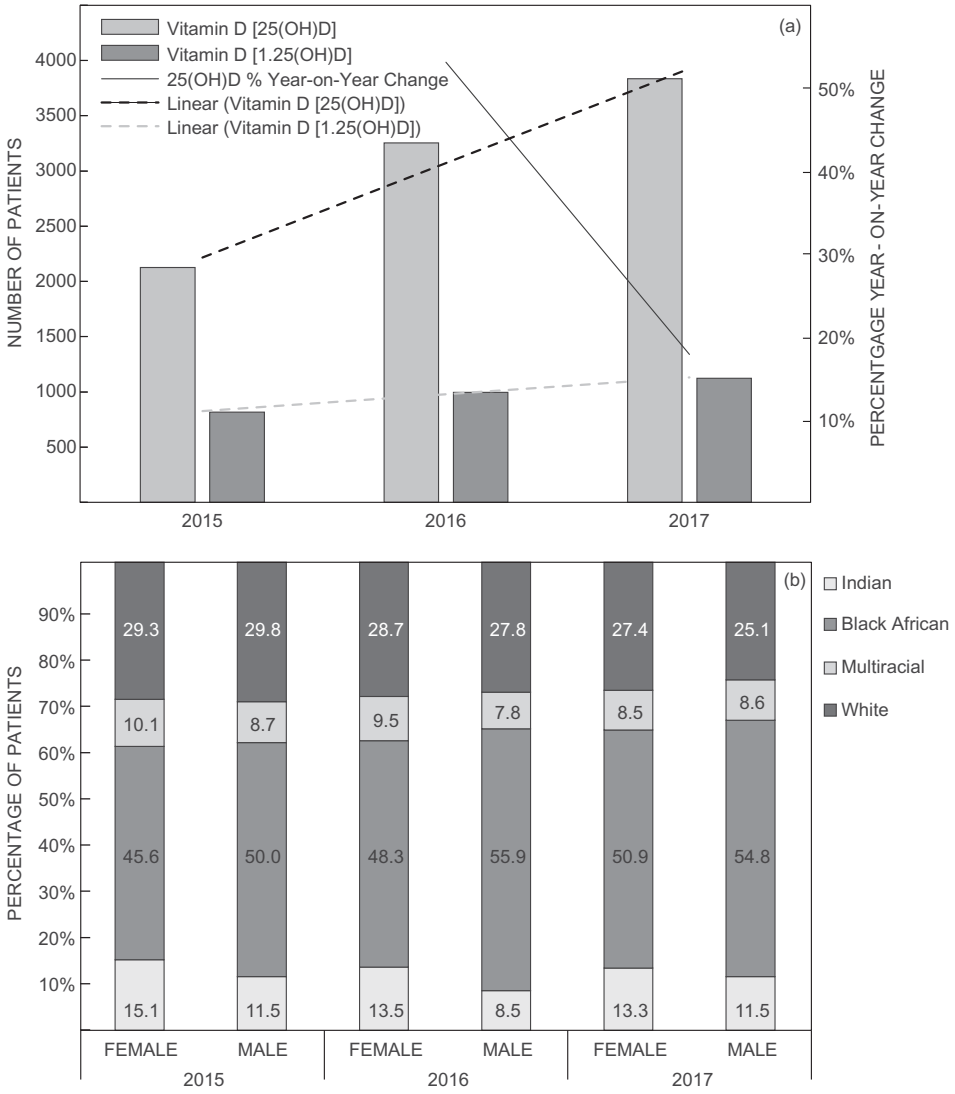

Figure 2: (A) Volume trends for 25(OH)D and 1,25(OH)$_2$D. (B) Test percentages per race and sex for 25(OH)D.

The LOWESS plots (Supplementary figures 1–3) showed an inverse relationship between the levels of 25(OH)D and the PTH. Our results indicated that the point at which circulating PTH concentration was maximally suppressed differed by race group. It was lowest in black African and highest in Indian patients. We could not estimate the threshold in the multiracial group due to a small sample size.

Table 1: Overall descriptive characteristics of study population

Factor	Race							
	White		Black African		Indian		Multiracial	
N (%)	2 387 (27.90)		3 884 (45.40)		875 (10.20)		765 (8.90)	
Sex	Female	Male	Female	Male	Female	Male	Female	Male
N (%)	1 778 (22.40)	609 (7.60)	2 782 (35.10)	1 102 (13.90)	698 (8.80)	177 (2.20)	573 (7.20)	192 (2.80)
Age (years)	58.08 ± 16.89		50.65 ± 16.88[1]		56.26 ± 15.46[2]		55.37 ± 16.51[3]	
Total 25(OH)D (nmol/l)	83.80 (59.20–112.00)		69.00 (47.20–95.20)[4]		69.20 (48.50–103.00)		79.50 (54.90–109.00)	
D2 (nmol/l)	11.70 (7.00–57.35)		7.00 (7.00–34.41)[4]		20.50 (7.00–65.20)		11.95 (7.00–57.10)	
D3 (nmol/l)	46.80 (27.30–72.20)		42.60 (26.70–64.00)		33.90 (20.95–51.45)		44.15 (27.35–66.30)	
1,25(OH)$_2$D (pmol/l)	134 (91–181)		133 (66–194)		125 (87–166)		137 (89–193)	

25(OH)D = hydroxyvitamin D, D2 = ergocalciferol, D3 = cholecalciferol, 1,25(OH)$_2$D = di-hydroxyvitamin D, data expressed as median and interquartile ranges except age, which is expressed as mean ± SD. [1]$p < 0.0001$ vs. all other race groups, [2]$p < 0.05$ vs. multiracial and white, [3]$p < 0.05$ vs. white, [4]$p < 0.0001$ across all other racial groups.

Table 2: Descriptive characteristics of study population by race and sex

Factor	Race, N (%)							
	White 2 387 (27.90)		Black African 3 884 (45.40)		Indian 875 (10.20)		Multiracial 765 (8.90)	
Sex, N (%)	F 1 778 (22.40)	M 609 (7.60)	F 2 782 (35.10)	M 1 102 (13.90)	F 698 (8.80)	M 177 (2.20)	F 573 (7.20)	M 192 (2.80)
Age (years)	60.20 ± 16.60	56.20 ± 17.00[1]	52.80 ± 16.90	46.90 ± 15.70[1]	58.70 ± 14.90	53.20 ± 15.90[1]	57.20 ± 16.30	50.90 ± 16.80[1]
Total 25(OH)D (nmol/l)	89.20 (62.90–123.50)	79.00[1] (57.30–100.40)	73.50 (50.50–101.50)	69.90[2] (48.40–96.80)	85.60 (56.80–118.70)	63.70[1] (44.10–86.10)	85.30 (58.70–121.50)	78.70[1] (52.50–107.45)
D2	26.80	7.00[1]	15.00	7.00[1]	42.10	7.00[1]	25.10	7.00[1]
(nmol/l)	(7.00–84.60)	(7.00–25.40)	(7.00–52.60)	(7.00–26.40)	(7.00–95.40)	(7.00–31.80)	(7.00–87.00)	(7.00–34.80)
D3	39.60	56.70[3]	39.10	48.20[3]	29.00	37.50[3]	38.90	48.90[3]
(nmol/l)	(23.60–65.60)	(31.20–77.80)	(23.90–60.60)	(30.30–69.70)	(17.30–46.40)	(22.80–56.40)	(24.60–61.90)	(30.50–73.40)
$1,25(OH)_2D$	128	113	141	81.0	104	128	113	–
(pmol/l)	(67–154)	(56–192)	(54–182)	(27–134)	(79–121)	(95–142)	(90–142)	
PTH	7.0	6.6	8.4	11.2	7.1	6.8	8.4	9.6
(pmol/l)	(4.8–11.7)	(4.1–22.6)	(4.7–17.8)	(3.6–35.9)	(4.1–10.3)	(3.3–29.1)	(5.1–17.0)	(4.5–33.9)
ALP	82	97[2]	96	97	79	90	83	85
(U/l)	(64–106)	(73–140)	(74–135)	(73–156)	(62–97)	(65–102)	(66–104)	(59–104)
With CKD, N (%)	117 (15.00)	44.00 (5.60)	311 (40.00)	180 (23.10)	29.00 (3.70)	13.00 (1.60)	59.00 (7.60)	23.00 (3.40)
Without CKD, N (%)	156 (23.60)	34.00 (5.10)	271 (41.10)	85.00 (12.80)	57.00 (8.60)	9.00 (1.30)	38.00 (5.70)	9.00 (1.80)

[1] $p < 0.0001$ vs. females across race, [2] $p < 0.05$ vs. females across race, [3] $p < 0.0005$ vs. females across race.

F = female, M = male, 25(OH)D = hydroxyvitamin D, D2 = ergocalciferol, D3 = cholecalciferol, $1,25(OH)_2D$ = di-hydroxyvitamin D, PTH= parathyroid hormone, ALP = alkaline phosphatase, - = no tests in this category, data expressed as median and interquartile ranges except age, which is expressed as mean ±SD. Reference intervals: ALP 42–98 U/l; PTH 1.6-6.0 pmol/l.

Table 3: Descriptive characteristics according to NAM categories

Factor	Deficient	Insufficient	Sufficient
Overall, N (%)	408 (5.50)	1314 (17.70)	5670 (76.70)
Race group, N (%):			
White	62 (3.20)	255 (13.10)	1 617 (83.70)
Black African	235 (6.70)[1]	712 (20.40)[1]	2 531 (72.90)
Indian	48 (6.60)[1]	133 (18.30)[1]	544 (75.10)
Multiracial	23 (3.60)	104 (16.30)	511 (80.10)
Sex N (%)			
Female	276 (5.20)	899 (16.90)	4 087 (77.90)
Male	127 (6.10)[4]	400 (19.40)[4]	1 525 (74.50)
Age category (%):	51.31 (±17.92)	53.30(17.16)	54.94 (17.34)[2,3]
< 30	7.90	20.60	71.50
30–59	5.70	19.30	75.00
60–74	4.20	16.80	78.80
> 74	5.60	17.20	77.00
CKD	5.80	19.00	75.10
Calcium (mmol/l)	2.06 (1.26–2.29)	2.22 (1.39–2.39)	2.33 (1.86–2.44)[3]
Inorganic phosphate (mmol/l)	1.08 (0.43–1.41)	1.13 (0.59–1.38)	1.09 (0.70–1.28)
PTH (pmol/l)	11.5 (1.3–32.2)	9.9 (0.9–25.7)	7.4 (1.7–14.0[3])
ALP (U/l)	116 (48–203)	97 (46–138)	86 (47–118)

CKD = chronic kidney disease, PTH = parathyroid hormone, ALP = alkaline phosphatase. Data expressed as percentages, median and interquartile ranges except age, which is expressed as mean ± SD. [1]$p < 0.0001$ for black African and Indian patients, [2]$p < 0.05$ vs. insufficient, [3]$p = 0.0001$vs. deficient, [4]$p < 0.009$ vs. deficient and insufficient females. Reference intervals: calcium 2.15–2.50 mmol/l; inorganic phosphate 0.78–1.42 mmol/l; ALP 42–98 U/l; PTH 1.6–6.0 pmol/l.

Discussion

We evaluated the number of 25(OH)D and 1,25(OH)$_2$D tests received from public sector hospitals and clinics from across South Africa over a three-year period. We noted an increase in test requests for both 25(OH)D and 1,25(OH)$_2$D, especially for samples from black African patients attending hospital. There was no change in median 25(OH)D levels over the period. Overall, the black African and Indian groups had the highest percentages of VDD and males were found to have significant lower levels of 25(OH)D as compared with females. The highest percentage of deficient and insufficient levels were found in patients less than 30 years of age and black African patients > 74 years. We further noted a provincial variation in the prevalence of deficiency, with more VDD found in the Free State.

Both 25(OH)D and 1,25(OH)$_2$D tests numbers demonstrated yearly increases, even though there was no significant change in median concentrations. Although there are no definitive testing criteria, routine widespread testing is not recommended in the general population.[6,11,15] The National Osteoporosis Foundation of South Africa (NOFSA) recommends that testing should be aimed at high-risk groups, specifically in bone health.[15] These include older adults, especially the frail, institutionalised elderly, those with osteoporosis, limited or ineffective sun exposure due to dark skin, clothing or hospitalisation, malabsorptive diseases, medication that interferes with vitamin D metabolism and, lastly, pregnancy with any of the risk factors as mentioned.[15] Increased research on the health benefits of vitamin D, in both the musculoskeletal system and other non-skeletal systems, and frequent media attention over the past years may have contributed to the volume trends.[3,4] Similar volume trends have been reported from countries across the globe, although the increases we have observed are far lower.[3,4] Recent studies suggest a low 25(OH)D level is an independent risk factor for COVID-19 infection and hospitalisation.[16,17]

We anticipate that this may lead to further increases in test requests. In South Africa, 25(OH)D and 1,25(OH)$_2$D are not subject to gatekeeping, which has been shown to curb overutilisation.[3,18]

There is wide variation in 25(OH)D concentrations reported from studies across South Africa, depending on the geographical location and the age.[1] Ours is one of the few that have reported concentrations by age and sex. Limited data is available for black African males as most studies included female participants only.[1,2] Contrary to the literature, we found a lower prevalence of VDD in females.[2,7] Females across all racial groups had a higher 25(OH)D level as compared with males. This was due to higher D_2 levels, suggesting possible supplementation. George *et al.* demonstrated that the dietary contribution in a healthy population was low in Africans as well as Indians.[2] While the difference may be due to diet, we postulate that as these are patients attending hospital, it is possibly from supplementation. Additionally, an increased prevalence of VDD was found in patients aged less than 30 years attending hospital, which is different from other local studies carried out in community-dwelling adults.[1,15] South Africa is known to have a high burden of infectious diseases such as HIV and tuberculosis as well as non-communicable diseases, and lower concentrations of 25(OH)D have been reported in patients with chronic diseases.[2] It is likely that underlying diseases may partly explain the increased prevalence in the younger age groups as no difference in median 25(OH)D_2 levels by race in the younger age group was observed. Our observation that 10.5% of black African patients above the age of 74 are deficient is significant. A number of South African studies have reported VDD in the elderly, though not by race group.[1,19,20] The elderly are prone to VDD for a number of reasons, including reduced cutaneous synthesis and daily sun exposure, as well as chronic diseases, and VDD may contribute to frailty and increased fracture risk.[1,21] Our data suggest that this group may benefit from testing as maintaining sufficient 25(OH)D levels has been shown to promote healthy ageing and reduction in frailty.[21]

Our results show that black African males and females had a higher proportion of CKD, as compared with other racial groups. Patients with CKD are prone to VDD, with early diagnosis and intervention leading to a reduction in CKD complications.[10,22] Using laboratory data, we were unable to determine the reason for most requests, but it appears that in black African patients monitoring of vitamin D levels in those with CKD may be one of the reasons. According to the 2017 KDIGO guidelines, in CKD, monitoring with 25(OH)D levels and not 1,25(OH)$_2$D is recommended.[9,10] Repeat testing should be individualised according to the baseline values and interventions.[10]

The PTH threshold was found to differ by race group. Aloai *et al.* have demonstrated that black females had a lower PTH threshold compared with white females (37 nmol/l vs. 59 nmol/l, respectively).[8] While we were unable to determine a specific cut-off, our observed threshold in black African

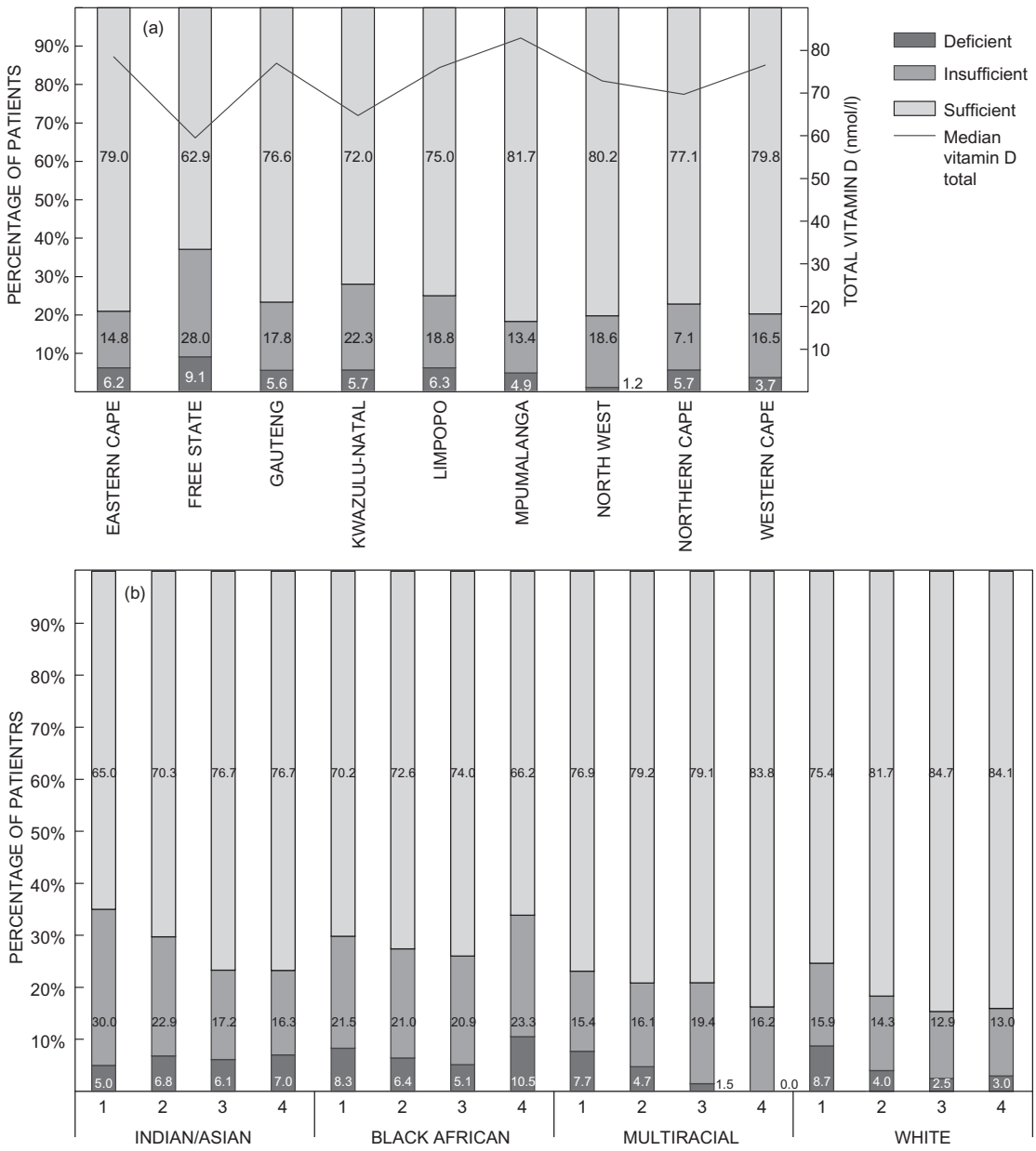

Figure 3: NAM categories by race and age. Data expressed as percentages, 1 ≤ 30 years, 2 = 30–59 years, 3 = 60–74 years and 4 ≥ 74 years.

patients was lower than that of white patients attending hospital. Thus, a single cut-off to define deficiency may not be appropriate in our setting as higher circulating PTH, secondary to deficiency, may have negative extra-skeletal effects.[8,22]

Overutilisation of 25(OH)D and/or 1,25$(OH)_2$D testing significantly increases healthcare costs.[3,11] Countries such as Canada have introduced specific indications for 25(OH)D testing, which resulted in an 80% reduction in test requests.[3,18] It is imperative that vitamin D testing, whether 25(OH)D and/or 1,25$(OH)_2$D, be based on evidence-based guidelines that offer testing for specific populations at higher risk of VDD. While routine testing to monitor 25(OH)D levels in patients taking supplementation for VDD is not recommended we need to determine what is appropriate locally.[11,23]

The strengths of our study include a large sample size and a data collection period of three years. However, our study had a number of limitations. We did not have clinical information, making it difficult to assess the reason for testing requests, as well as profiling. The majority of the data are from patients seeking hospital care in Gauteng, and we did not include 25(OH)D and 1,25$(OH)_2$D tests that were done at all NHLS laboratories or the private sector. Therefore, the yearly volume increases for the country may be different from those reported here. Our findings are not applicable to the entire population and are not representative of a healthy population. The data are from 2015–2017 and current trends may have changed. We were unable to further describe the vitamin D profiles in CKD patients due to a small sample size. Finally, racial groups were determined by imputation, which has some limitations.

Conclusion

Our findings suggest that VDD varies by age and race group, with proportionally more black African and Indian patients attending hospital, deficient and insufficient. In addition, younger patients and elderly black African patients attending hospital may be risk groups for VDD. Further work to determine the aetiologies of VDD in these groups is are needed. It may be due to diseases that may require temporary supplementation or

other causes unrelated to illness, which would require long-term treatment. Additionally, further work is required to understand the appropriate cut-off levels to define VDD in our populations. Clear testing guidelines are needed to curb test overutilisation. It might be of value to consider implementing test gatekeeping.

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