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Screening pre-diabetes and obese women in an early stage of renal dysfucntion from serum 25- hydroxy vitamin D and serum parathormone levels with age, body mass index and fast plasma glucose

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Abstract

It is known that vitamin D may affect renal homeostasis and is inversely correlated with serum parathormone (PTH). We proposed some classes of levels of serum 25- hydroxyvitamin D (25(OH)D) and PTH, we wondered whether fast plasma glucose concentrations or less costly criterion as Age or BMI could be used to predict classification of each woman of our cohort in classes of serum 25(OH)D/PTH concentrations. Measurements of serum 25(OH)D and serum PTH were done, among 165 adult African migrants women. ROC analysis was used to identify serum 25(OH)D and serum PTH thresholds. Machine-learning tools were performed to predict classes of 25(OH)D and serum PTH levels from age, body mass index and fast plasma glucose. A threshold of serum 25(OH)D of 50 ± 5 nmol/L and serum PTH of 44 ± 6 ng/L level was found with a sensitivity of 86%, a specificity of 83%. We identified 40% of the sample as forties women, obese and pre-diabetic in an early stage of kidney disorders. Estimation with Fast Capillary Glucose measurement instead of Fast Plasma Glucose could be a less costly method to screen glucose and vitamin D status among migrant women.

Introduction

Vitamin D is required for efficient absorption of dietary calcium and for good health. It is obtained from sun exposure and diet and is converted in the liver to hydroxycholecalciferol (25(OH)D), the primary storage form of the vitamin. Subsequently 25(OH) D is converted in the kidney into its biologically active form, 1,25 dihydroxyvitamin D (1,25(OH)$_2$D). When serum calcium declines, parathyroid hormone (PTH) increases, which results in osteoclast activity and release of calcium from bone. PTH also acts on the kidney to stimulates the conversion of 25(OH)D to 1,25(OH)$_2$D. In turn, 1,25(OH)$_2$D increases intestinal calcium absorption. Reduction in 25(OH)D levels is associated with impaired calcium absorption and a compensatory increase in the level of PTH which, in turn, stimulates bone resorption [1]. Usually, vitamin D status is defined according to serum 25(OH)D concentration [2,3]. There is a significant inverse relationship between circulating 25(OH)D and serum PTH. When 25(OH)D availability declines, serum 1,25(OH)$_2$D declines, and this results in reduced calcium absorption, a transient decline in serum calcium concentration, and stimulation of PTH secretion known as secondary hyperparathyroidism, conventionally defined as a PTH level >65 ng/L [4]. Although, there is no universal consensus as to the optimum threshold limit of serum 25(OH)D the most commonly used way to assess that serum 25(OH)D cut-off is based on the negative relationship between serum 25(OH)D and PTH levels and it is proposed that it is the serum concentration of 25(OH)D at which PTH levels are minimized [5]. Then, in many studies non parametric methods as regression models were used to estimations reliable serum 25(OH)D cut-offs. However this method often implied to exclude a huge part of the sample [5-7]. Vitamin D status is defined by serum 25(OH)D con- centration [1,2], which is influenced in turn by various factors including latitude, skin pigmentation, dietary and calcium intake [3]. Recently effects of vitamin D on renal function were reported, emerging evidence suggests that the progression of renal disorders and many of the cardiovascular complications may be linked to low vitamin D status [8]. African population is especially concern as a population with strong prevalence of low vitamin D status [9]. Our purpose was to determine classes of serum 25(OH)D/PTH levels with use of 25(OH)D threshold below which PTH concentrations increases. Then, in our sample, we wondered whether FPG measurement or less costly criterion as Age or BMI could be used for each African migrant women for the prediction of her class of serum 25(OH)D/PTH levels.

Methods

Patients

The study was conducted in a Community Clinic lo- cated in eastern Paris at latitude 48.5N. The inclusion criteria specified adult African migrant women. Patients were excluded if younger than 18 years old,

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had a body mass index (BMI) >30, or if their medical history might influence their serum PTH concentration (hyper- or hypocalcemia, renal insufficiency, medical treatment: bisphosphonates, anti-convulsants, lithium). In France, a migrant is defined as someone who was born in a foreign country as a non-French citizen. One hundred sixty-five migrant adult women with a mean age of 38.6 ± 9.9 years were included in the study between February 2008 and November 2009. This study was approved by the Independent Ethics Committee of Paris IV and all participants provided written informed consent.

Calcium intake

We used a food-frequency type self-assessment questionnary to estimate the daily calcium intake of each patient [10].

Measurements

Serum 25(OH)D was measured using chemiluminescence methodology (Diasorin, LIAISON®) [11] by the Pasteur Cerba laboratory. The test interval measure was between 10 and 350 nmol/L. Over all seasons of the year and for both genders, 25(OH)D norms [12] were as follows: Recommended levels: 75-200 nmol/L (30-80 µg/L), Insufficiency: 25-75 nmol/L (10-30 µg/L), Deficiency: <25 nmol/L (<10 µg/L). Functional sensitivity was 17.5 nmol/L with interassay coefficients of variation (CVs) of 12.9%. PTH was measured by chemiluminescence using a LIAISON® N-tactTM PTH test. The test interval measure was be- tween 1 and 2,000 cm/L and normal PTH levels were <51 cm/L [13]. Samples were collected in dry tubes for serum 25(OH)D, in tubes with EDTA for PTH. FPG was measured with hexokinase technic -Cobas c501 norms were 4.11-5.89 mmol/L. Hba1c were measured with high pressure chromatography-D10 Biorad norms were <6. Serum Phosphorus was measured with phosphomolybdate technic-Cobas c501 norms were 27-45 mg/L. Serum alkaline phosphatases were measured with IFCC colometric technic-Cobas c501 norms were 40-130 U/L. Renal function was estimated by clearance creatinine, calculated using the Cockcroft and Gault equation and serum creatinine. After an overnight fast, blood samples were drawn from 8.00 to 10.00 a.m. for measurement of 25(OH) D, PTH, and calcium. Urines creatinin was measured with Jaffe technic-Cobas c501 norms were 7-14 mmol/day. Urines phosphorus was measured with phosphomolybdate–Cobas c501 norms were 13-42 mmol/day. Renal tubular phosphate handling was assessed for each patient as the ratio of the maximum rate of tubular phosphate reabsorption (TmP) to the glomerular filtration rate (GFR) as TmP/GFR=serum phosphate -(urines phosphate x serum creatinin/urines creatinin), norms were 2,8-4,4 mg/dL [14].

Statistical analysis

Gaussian mixture model: The Expectation-Maximization (EM) algorithm [15] was used to estimate FPG distributions as a Gaussian mixture.

Regression analysis: We used non-parametric kernel regression method implemented in the 'npreg' function of the Hayfield *et al.* (np) package [16] for the R software version 2.10.0.

ROC analysis: The diagnostic performance of a test, or the accuracy of a test to discriminate diseased cases from normal cases is evaluated using ROC curve analysis [17,18]. In practice the AUC performs very well and is often used when a general measure of predictiveness is desired [19]. In this study, we tested all serum 25 (OH)D values in the range of class 1 levels, 38-60 nmol/L, previously estimated with Gaussian mixture model fitted for serum 25(OH)D distributions. We noted (x) as a variable value. We choose PTH values in the Gaussian mixture ranges. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. We took the best threshold point [20].

Machine learning: We used Adaboost [21,22] to estimated classes of 25 (OH)D/PTH. Boosting is an approach to machine learning based on the idea of creating a highly accurate prediction rule by combining many relatively weak and inaccurate rules. Adaboost algorithm is particular because it needs no prior knowledge of the accuracies of the weak hypotheses. It adapts to these accuracies and generates a weighted majority hypothesis in which the weight of each weak hypothesis is a function of its accuracy. Based on 20 repetitions of 10-fold cross validation (CV), Adaboost algorithm was used to predict from data observed classification of patients in different classes of serum 25(OH) D levels and serum PTH levels defined with our 25(OH)D/PTH threshold as below. We choose three strong predictor variables selected as FPG, BMI and age. We used Adaboost algorithm implemented in R software version 2.10.0.

Results

Basic statistics

Shown in Table 1.

ROC analysis

In the whole sample, ROC analysis found a decision threshold point of serum 25(OH)D of 65 nmol/L and PTH of 44 ng/L with a sensitivity of 86%, a specificity of 81%, a positive predictive value of 96% and a negative predictive value of 57%. When laboratory norms were used the best point of decision was of a sensitivity of 58%, a positive predictive value of 100%, a negative predictive value of 0% and a specificity was not calculable.

Classes of 25(OH)D/PTH levels (Tables 2 and 3).

We found four classes of serum 25(OH)D and serum PTH concentrations. We noticed that there was two classes of levels with a weak relationship between serum 25(OH)D and serum PTH as class 4 (serum 25(OH)D > 65 nmol/L, serum PTH ≥ 44 ng/L) and class 2 (serum 25(OH)D ≤ 65 nmol/L, serum PTH <44 ng/L). And two classes of levels with a strong relationship between serum 25(OH)D and serum PTH concentrations as class 1 (serum 25(OH)D ≤ 65 nmol/L, serum PTH ≥ 44 ng/L) and class 3 (serum 25(OH)D >65 nmol/L, serum PTH < 44 ng/L). FPG distributions.

Clearance creatinin distributions

The EM algorithm provided the estimates of four Gaussian bell curves: subclass R (mean1=97.224 ± 1.829, component weight: 1%), subclass E (mean=111.375 ± 5.743, component weight: 48.5%), subclass I (mean=117.224 ± 1.829, component weight: 33.2%), subclass N (mean = 75.733 ± 8.636, component weight: 8%).

Table 1. Basic statistics.

African migrants women	(n=165)
Mean age	38.6 ± 9.9
Clearance creatinine (ml/min)	119.32 ± 36
Daily Calcium Intakes (mg/day)	800.59 ± 303.16
Baseline calcium intakes	
Milk products	50%
Mineral waters	14%
Others	36%

Table 2. Means of 25(OH)D/PTH level classes.

***n*=165**	**Class 1 (40 %) n_1=66**	**Class 2 (32 %) n_2=52**	**Class 3 (15 %) n_3=25**	**Class 4 (13 %) n_4=22**
Calcium intakes (mg/d)	635.42 ± 24.13	482.5 ± 28.99	1137.47 ± 31.34	1783.28 ± 31.16
Age (years)	43 ± 15	37 ± 6	26 ± 7	57 ± 16
BMI (kg/m^2)	26.48 ± 7.54	21.5 ± 5.4	23.71 ± 0.66	33.45 ± 6.33
FGP (mg/dL)	530 ± 89	467 ± 44	494 ± 11	542 ± 61
HBA1C	5.75 ± 0.66	5.66 ± 0.31	6.20 ± 0.95	7.07 ± 2.19
Serum Creatinin (mg/L)	11.61 ± 1.54	7.52 ± 1.35	6.7 ± 0.82	9.62 ± 2.51
Clearance Creatinin (ml/mn)	60.31 ± 13.70	81.25 ± 26.87	92.53 ± 30.24	70.72 ± 14.59
Serum Phosphore (mg/L)	29.2 ± 2.2	34.6 ± 2.4	38.4 ± 1.7	32.3 ± 2.8
Serum Alkalin Phosphatases	95 ± 16.26	58.7± 12.14	62 ± 24.11	75 ± 5.76
Serum PTH (ng/L)	77.53 ± 14.21	32.42 ± 4.40	21.98 ± 4.02	60.18 ± 3.43
Serum 25(OH)D (nmol/L)	31.38 ± 14.71	41.62 ± 8.32	80 ± 7.07	88.02 ± 21.78
Urine Creatinin (mmol/d)	16.17 ± 3.71	11.98 ± 5.81	7.51 ± 3.10	17.57 ± 10.22
Urine Phosphore (mmol/d)	26.24 ± 9.92	11.35 ± 0.63	3.24 ± 0.83	15.43 ± 2.37
TmP/GFR (mg/dl)	2.80 ± 0.53	3.17 ± 0.57	3.49 ± 0.32	3.17 ± 0.40

Table 3. Comparing class means: Wilcoxon tests with significant p-values.

	Class1 *vs.* Class2	**Class1 *vs.* Class 3**	**Class1 *vs.* Class 4**	**Class 2 *vs.* Class 3**	**Class 2 *vs.* Class 4**	**Class 3 *vs.* Class 4**
Calcium intakes (mg/d)	$m_1 > m_2$ (<0.01)	$m_1 < m_3$ (<0.01)	$m_1 < m_4$ (< 0.01)	$m_2 < m_3$ (<0.01)	$m_2 < m_4$ (< 0.01)	$m_3 < m_4$ (< 0.01)
Age (years)	$m_1 > m_2$ (0.03)	$m_1 > m_3$ (<0.01)	$m_1 < m_4$ (< 0.01)	$m_2 < m_3$ (<0.01)	$m_2 < m_4$ (< 0.01)	$m_3 < m_4$ (< 0.01)
BMI (kg/m^2)	$m_1 > m_2$ (<0.01)	$m_1 > m_3$ (0.01)	$m_1 > m_4$ (< 0.02)	$m_2 > m_3$ (0.06)	$m_2 < m_4$ (0.03)	$m_3 < m_4$ (< 0.01)
FPG (mg/dL)	$m_1 > m_2$ (< 0.01)	$m_1 > m_3$ (<0.01)	$m_1 < m_4$ (0.08)	$m_2 < m_3$ (< 0.01)	$m_2 < m_4$ (0.01)	$m_3 < m_4$ (0.08)
HbA1C (%)	$m_1 > m_2$ (0.79)	$m_1 < m_3$ (0.07)	$m_1 < m_4$ (0.06)	$m_2 < m_3$ (0.04)	$m_2 < m_4$ (0.04)	$m_3 < m_4$ (<0.01)
Serum Creatinin	$m_1 > m_2$ (<0.01)	$m_1 < m_3$ (0.20)	$m_1 < m_4$ (0.11)	$m_2 < m_3$ (0.30)	$m_2 < m_4$ (0.22)	$m_3 < m_4$ (<0.01)
Clearence Creatinin	$m_1 < m_2$ (0.10)	$m_1 > m_3$ (0.28)	$m_1 > m_4$ (0.01)	$m_2 > m_3$ (<0.01)	$m_2 > m_4$ (<0.01)	$m_3 < m_4$ (0.53)
Serum phosphore	$m_1 < m_2$ (0.30)	$m_1 < m_3$ (0.07)	$m_1 < m_4$ (0.23)	$m_2 < m_3$ (0.15)	$m_2 < m_4$ (0.69)	$m_3 > m_4$ (0.50)
Serum alkalins phosphates	$m_1 > m_2$ (<0.01)	$m_1 > m_3$ (<0.01)	$m_1 < m_4$ (<0.01)	$m_2 < m_3$ (0.09)	$m_2 < m_4$ (0.03)	$m_3 < m_4$ (0.02)
Serum PTH (ng/L)	$m_1 < m_2$ (< 0.01)	$m_1 < m_3$ (< 0.01)	$m_1 > m_4$ (<0.01)	$m_2 < m_3$ (0.03)	$m_2 < m_4$ (< 0.01)	$m_3 < m_4$ (< 0.01)
Serum 25(OH)D (nmol/L)	$m_1 < m_2$ (< 0.01)	$m_1 < m_3$ (< 0.01)	$m_1 < m_4$ (< 0.01)	$m_2 < m_3$ (< 0.01)	$m_2 < m_4$ (< 0.01)	$m_3 < m_4$ (< 0.01)
Urinary Creatinin	$m_1 < m_2$ (0.75)	$m_1 > m_3$ (0.08)	$m_1 > m_4$ (<0.01)	$m_2 < m_3$ (< 0.01)	$m_2 < m_4$ (< 0.01)	$m_3 < m_4$ (0.06)
Urinary Phosphore	$m_1 < m_2$ (<0.01)	$m_1 > m_3$ (<0.01)	$m_1 < m_4$ (0.03)	$m_2 > m_3$ (<0.01)	$m_2 < m_4$ (<0.01)	$m_3 < m_4$ (<0.01)
TmP/GFR (mg/dl)	$m_1 < m_2$ (0.07)	$m_1 < m_3$ (<0.01)	$m_1 < m_4$ (0.03)	$m_2 < m_3$ (0.06)	$m_2 > m_4$ (0.08)	$m_3 > m_4$ (0.04)

Table 4. Performance of Adaboost algorithm for 25(OH)D/PTH classes data based on 20 Repetitions of 10-fold CV (S.D. in parentheses).

Accuracy	**Sensitivity**	**Specificity**	**Positive Predictive value**	**Negative Predictive value**
.998 (.002)	1.00 (.002)	.994 (.003)	.993 (.001)	.998 (.007)

Adaboost algorithm

We found age, BMI and FPG as stronger criterions to discriminate each patient of our sample. Classes of 25(OH)D/PTH levels were predicted with an error rate of less than 1% (Table 4).

Discussion

We chose to examine this population as it was characterized by low dermal synthesis of vitamin D due to high melanin pigmentation [23], low 25(OH)D levels, and reactive increases in PTH, which are highly prevalent in African migrants living in Northern latitudes [24]. Furthermore recent studies have shown that elevated PTH levels are associated with increased cardiovascular risk in the general population [25,26] and it is known that high PTH concentrations lead to a decreased of the kidney function [27]. New evidence has now established that the role of vitamin D is no longer solely restricted to its classical function of maintaining calcium and phosphate homeostasis, Vitamin D appears to play a more extensive role in a variety of tissues including the renal, cardiovascular systems [8]. Thus, identifying a 25(OH)D threshold below which PTH concentrations are elevated might be of use in estimating cardiovascular or renal disorders risk due to high PTH concentrations.

Calcium sufficiency

In our study, the daily calcium intake of African women, estimated with 20% precision [10], was higher than 400 mg/day. This estimate was higher than the 300 mg/day reported by Prentice *et al.* among African women living in Africa [28-31], and close to the 900 mg/day recommended for French women younger than 55 years old [32]. However, Heaney *et al.* estimated that African American women require 300 mg less calcium per day compared to white women [33], which suggests that the average calcium daily intake of African women in our sample was sufficient.

Serum 25 (OH)D and Serum PTH cut-offs

In the litterature, the serum 25(OH)D threshold corresponding with the PTH inflection point has been interpreted as indicative of optimal calcium homeostasis and proposed to defining recommended vitamin D intake [5,34]. According to Steingrimsdottir *et al.*, one limit

to this approach is because there is considerable variation in the level of 25(OH)D associated with any given serum PTH concentration, and reported threshold levels have varied greatly from 8 to 44 ng/L [35]. In our study, serum PTH cut-offs found were in similar PTH thresholds levels reported. According to Sahota *et al.,* as low 25(OH)D status is defined biochemically as the degree of low serum 25(OH)D resulting in an increase of PTH levels, it may be more appropriate to include a threshold level of PTH in the disease definition [36]. In our study we found PTH cut-offs within conventional normal range. According to Sahota *et al.* [36], it is evident that in the presence of low 25(OH) D status, the threshold defining secondary hyperparathyroidism is probably in the upper tertile of the laboratory reference range and that defining 'functional low PTH levels' in the lower tertile. It was similar to ours results. In our study, ROC analysis highlighted some interesting values. We noticed that values 25(OH)/PTH cut-offs found were respectively similar to value of mean 25(OH)D classes 1-2 and to value of mean PTH classes A-B estimated with our Gaussians mixtures model [7]. Our previous 25(OH)D/PTH curve showed serum 25(OH) D thresholds corresponding to points of inflection of PTH levels similar to 25(OH)D/PTH cut-offs estimated with ROC analysis.

Most authors used regression models to estimate serum 25(OH) D thresholds and to get more accuracy it need frequently to exclude as outliers a significant part of patients, an average of 40% of the sample [5-7]. In our previous study, we had to remove 30% of the sample to increase estimations accuracy with Kernel regression model otherwise it was not reliable. In this study, the 25(OH)/PTH test was valuable when 4% of the sample was removed. This suggests that ROC analysis could be equally applicable as regression models. Moreover, ROC graphs are commonly used in medical decision-making and in recent years have been used increasingly in machine learning and data mining research [37]. With robust non parametric ROC analysis we estimated significant serum 25(OH)D/PTH thresholds points without removed any outliers or very few. This appears to be the major difference compared with our previous Kernel regression model method.

Classes of behaviors

It is well-known that sunlight it's the principal source of vitamin D and its increases serum 25(OH)D concentrations through the skin. In our study we found classes 3 and 4 of women with high serum 25(OH)D levels suggesting they had more daylights exposition than classes 1 and 2 of women with low serum 25(OH)D levels. There is no effect of age on 25(OH) D concentrations while in human serum PTH concentrations increases with aging [38]. It could partly explain high serum PTH levels in the oldest classes of women and low serum PTH levels in the youngest classes of women.

Classes of renal status

We noticed that estimations of means of our quadruple Gaussian of creatinin clearance distributions were similar ranges of those of classification of chronic kidney diseases (CCKD) [39]. As we did not estimate the similar lower ranges of CCKD stage 5, it was agree that no women with end stage renal disease were selected in our sample. According to Falch *et al.* there a relation between age and serum phosphate levels in adults, serum phosphate levels decline with age, except for a transient increase during the peri-menopausal period in women [40]. Cirillo *et al.* have shown that the decrease in the TmP:GFR ratio with age was similar to that in serum phosphate levels, the age-associated decline in serum phosphate levels was not associated with hypocalcemia and hypocalciuria, nor with indexes of protein and salt intake [41]. The authors reported that the increase in serum phosphate levels in women between the ages of 45 and 54 years was probably not related to age itself, but rather to menstrual status. In our study forties women in class 1 had a not normal decreased TmP:GFR ratio and that could suggested possible renal tubular defects . According to Malluche *et al.* in the early stages of renal failure, hyperparathyroidism develops as a compensatory mechanism to control serum levels of phosphorus [42]. As kidney dysfunction progresses this ability to maintain mineral homeostasis is lost leading to the development of renal diseases. Then at least, women of our class 1 could be suspected to be in an early stage of kidney dysfunction. Leibovitch *et al.* reported that serum alkaline phosphatase maybe a marker for involvement of the kidneys in pathological processes and increased serum alkaline phosphatase is a possible indicator of renal damage [43]. In our sample, among classes of low serum 25(OH)D concentrations, class 1 of forties women had significant highest serum alkaline phosphatase levels. In our study, when we took in account BMI [44] and definition of glucose disorders based on HbA1c classification [45] we determined class of low serum 25 (OH)D concentrations and high serum TSH levels, as class 1 of oldest forties women, obese and pre-diabetic in an early stage of kidney disorders. Class of high serum 25(OH)D levels and low serum PTH concentrations determined as class 4 of fifties overweight and diabetic women. We classified younger forties and thirties subjects as classes of slender women with low serum PTH concentrations and with a high risk for developing glucose disorders in the future.

Discriminant factors of classes of levels and machine learning. In our study we used three criterions that classified whole sample, as FPG, BMI and age. From women FPG measurement and using boosting data method as Adaboost we estimated classes of serum 25(OH)D and serum PTH levels. Each patient was classified precisely in a one of the four classes of 25(OH)/D levels defined.

Limitations

We noticed that diagnostic of chronic renal diseases need confirmation with at least two different and closely following control of the renal function. In this study we did not practice second blood and urinary analysis of renal function. Our results could be understand as focus on renal function should be a health priority in medical monitoring program among African migrant women. Note that there are non-calcemic effects of vitamin D in other biological metabolisms which likely need higher 25(OH)D concentrations than those required to maintain PTH secretion [46]. Therefore, 25(OH)D threshold of 65 nmol/L should not be interpreted as optimum vitamin D status. Although the importance of preventing undue increases in serum PTH for bone health is generally recognized, evidence is lacking for identifying the exact levels that may be detrimental [47]. Then, serum PTH cut-off of 44 ng/L should not be interpreted as absolute PTH cut-off.

Conclusion

From our sample of 165 calcium-sufficient African migrant women living in Paris, ROC analysis found a 25(OH)D threshold of 65 nmol/L and PTH of 44 ng/L in the whole sample. We identified 40% of the sample as forties women, obese and pre-diabetic in an early stage of kidney disorders. With our model of machine learning From Age, Body Mass Index and Fast Plasma Glucose we classified each patient of our sample in different classes of 25 hydroxyvitamin D and serum parathormone levels with a sensitivity of 99%, a specificity of 99%, a true positive value of 98% and a true negative value of 98%. Estimation with Fast Capillary Glucose measurement instead of Fast Plasma Glucose could be a less costly method to screen glucose and vitamin

D status among African migrants women. Estimating vitamin status and glucose status in others samples of population might be of interest.

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