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Serum 25-hydroxy-vitamin D_3 concentrations increase during tuberculosis treatment in Tanzania

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SUMMARY

SETTING: Vitamin D deficiency is associated with susceptibility to active tuberculosis (TB) in many settings. In vitro studies and studies on human volunteers showed that two of the first-line anti-tuberculosis drugs, isoniazid and rifampicin, reduce 25-hydroxy vitamin D (25[OH]D) concentrations.

OBJECTIVE: To study changes in vitamin D status during treatment of Tanzanian hospitalised patients with pulmonary TB (PTB).

DESIGN: We compared serum 25[OH]D concentrations in 81 Tanzanian PTB patients before and after 2 months of treatment.

RESULTS: Median serum 25[OH]D concentrations increased from 91 nmol/l at baseline to 101 nmol/l after 2 months of TB treatment (median increase 6.0 nmol/l, IQR −0.7–25.0, $P = 0.001$). Median serum parathyroid hormone concentrations increased from 1.6 to 2.0 pmol/l (median increase 0.46, IQR −0.2–1.1, $P < 0.001$).

CONCLUSION: 25[OH]D serum concentrations increased during the first 2 months of TB treatment in 81 PTB patients in northern Tanzania. Improved dietary intake and increased sunlight exposure may have contributed to the increased 25[OH]D concentrations.

KEY WORDS: anti-tuberculosis treatment; *Mycobacterium tuberculosis*; nutrition; rifampicin; isoniazid

IN THE PRE-ANTIBIOTIC ERA, Vitamin D from cod liver oil and from sun exposure (in sanatoria) was used for treating tuberculosis (TB).[1,2] Several observational studies indicate that vitamin D deficiency plays a role in susceptibility to TB.[3,4] Polymorphisms in the vitamin D receptor gene have been associated with delayed treatment response.[5,6]

Vitamin D is metabolised by several cytochrome P450 (CYP450) enzymes. Vitamin D_3 is synthesised in the skin during exposure to sunlight and is also available in the diet, mainly from oily fish or fortified foods (Figure). Vitamin D_3 is hydroxylated in the liver to 25-hydroxy-vitamin D_3 (25[OH]D), the accepted indicator of vitamin D status, which is further hydroxylated to 1,25-dihydroxy-vitamin D ($1,25[OH]_2D$), under the regulation of the parathyroid hormone. The kidneys play a major role in this hydroxylation step. Neither vitamin D_3 nor its biologically active metabolite $1,25[OH]_2D$ have direct antimycobacterial action, but $1,25[OH]_2D$ induces in vitro anti-tuberculosis activity in both monocytes[10] and macrophages.[11] Activated macrophages can convert 25[OH]D to $1,25[OH]_2D$.[1,12] Several CYP450 are involved in vitamin D metabolism: vitamin D_3 25-hydroxylase (CYP27A1), 25-hydroxyvitamin D_3 1-alpha-hydroxylase (CYP27B1) and 1,25-dihydroxyvitamin D_3 24-hydroxylase (CYP24A1) are key enzymes in vitamin D metabolism.[7,8]

Two of the standard first-line anti-tuberculosis drugs, isoniazid (INH) and rifampicin (RMP), are known for inhibiting and inducing CYP450 activity, respectively, and can affect vitamin D metabolism. INH reduces 25[OH]D and $1,25[OH]_2D$ concentrations by the inhibition of 25-hydroxylase, as has been shown in in vitro studies, animal studies and human volunteers.[7,9,13,14] RMP is a strong inducer of CYP3A4,[15] which is a vitamin D 24- and 25- hydroxylase.[8] Induction of these enzymes increases the enzymatic conversion of 25[OH]D to the inactive metabolite $24,25[OH]_2D$ and results in decreased 25[OH]D and $1,25[OH]_2D$ concentrations, as shown in studies in human volunteers.[14,16] Combined use of INH and RMP reduces 25[OH]D and $1,25[OH]_2D$ concentrations in both human volunteers and TB patients.[14]

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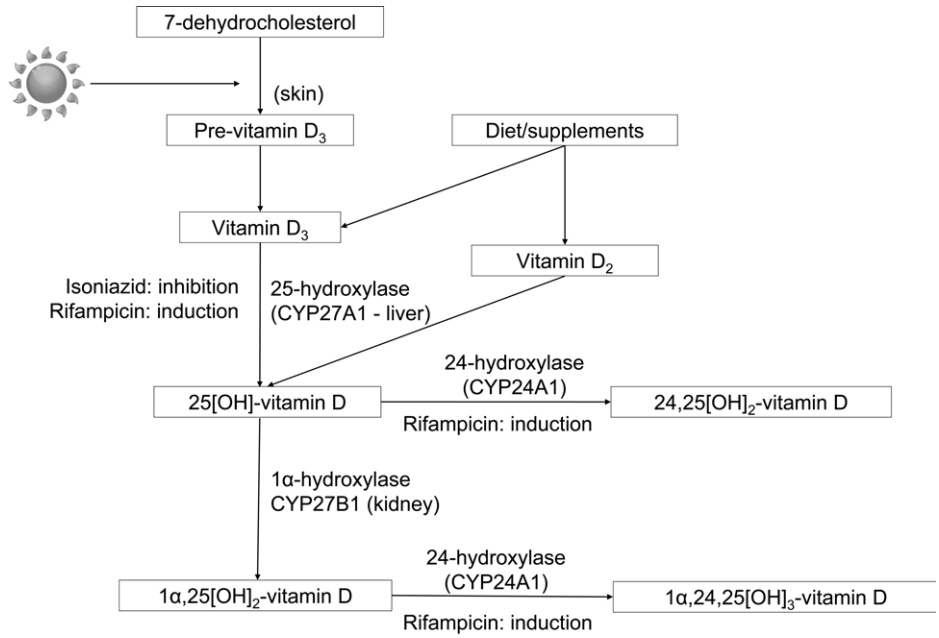

Figure Vitamin D metabolism. Isoniazid inhibits and rifampicin induces several steps in the vitamin D metabolism.[7–9]

The exact effect of INH and RMP on 25[OH]D concentrations in TB patients is controversial, however, because decreased[14,16] and increased 25[OH]D concentrations[17] and no evidence of effect[18] have been reported.

The human immunodeficiency virus (HIV) is associated with low vitamin D concentrations and may therefore be a confounding factor in TB drug-induced changes in 25[OH]D.[19] As HIV co-infection is common in sub-Saharan African TB patients, it is important to determine the effect of TB drugs on vitamin D concentrations in TB patients in this region.[20] We therefore determined 25[OH]D concentrations in Tanzanian pulmonary TB (PTB) patients before and after 2 months of treatment.

STUDY POPULATION AND METHODS

Study population

Study participants were recruited with the support of the Kilimanjaro Christian Medical Centre in Moshi at the Kibong'oto National Tuberculosis Hospital (KNTH), a referral centre for TB in Sanya Juu, northern Tanzania. In KNTH, TB patients are admitted during the first 2 months of treatment. All PTB patients aged >18 years who started standard first-line TB treatment between April 2007 and June 2008 were included in this study.

The study was approved by the Tanzanian National Institute for Medical Research; all patients gave written informed consent.

Tuberculosis treatment

Patients were diagnosed and treated according to guidelines of the Tanzanian National Tuberculosis and Leprosy Programme. Patients with a body weight < 50 kg received 225 mg INH, 450 mg RMP, 1200 mg pyrazinamide (PZA) and 675 mg ethambutol (EMB) per day, whereas those > 50 kg received 300 mg INH, 600 mg RMP, 1600 mg PZA and 900 mg EMB per day. Drugs were given as fixed-dose combination tablets (Novartis®, Basel, Switzerland). All patients received directly observed treatment (DOT).

Clinical chemistry

Before the start of TB treatment and after 2 months of treatment, blood samples were collected, centrifuged and the serum stored at −20°C until analysis.

Serum concentrations of 25[OH]D_3 and parathyroid hormone (PTH) were measured on a Cobas E601 Analyzer (Roche Diagnostics, Basel, Switzerland) according to the manufacturer's instructions. Serum concentrations of calcium, albumin, phosphate and magnesium were measured with a Beckman-Coulter Unicel DxC 880i Analyzer (Roche) using photometric techniques. Interrun coefficients of variation (CVs) for 25[OH]D were respectively 5.4% and 3.8% at 51 and 103 nmol/l.

Serum albumin concentration was measured as an indicator for nutritional status, and PTH as an indicator for 1,25$[OH]_2$ vitamin D production. We were not able to measure the 1,25$[OH]_2$D concentrations due to the small volume of serum available. Albumin-corrected calcium concentrations were calculated as follows:

$$\text{calcium} + 0.02 \times (40 - [\text{albumin}]).$$

Vitamin D deficiency and vitamin D insufficiency were defined as 25[OH]D concentrations < 50 nmol/l and between 50 and 75 nmol/l, respectively.[21]

Statistical analysis

We report mean values ± standard deviation (SD) or mean (95% confidence interval [CI]) unless indicated otherwise. Variables that were not normally distributed are presented as median (interquartile range [IQR]). A paired *t*-test was used to assess differences in means measured before and after 2 months of treatment; the Wilcoxon signed rank test was used for parameters that were not normally distributed. As smear conversion at 2 months is associated with treatment outcome,[22] we compared the 2-month sputum smear conversion rate between patients with and those without baseline vitamin D deficiency. All analyses were performed using SPSS for Windows (version 16.0, Statistical Package for the Social Sciences, Chicago, IL, USA).

RESULTS

The characteristics of the 81 PTB patients included in this study are shown in Table 1. We determined serum concentrations of 25[OH]D and PTH in all patients, whereas serum concentrations of calcium, albumin, phosphate and magnesium were determined in 48 patients only due to insufficient serum volume. At baseline, one patient (1%) had vitamin D deficiency and 13 patients (16%) had an insufficient vitamin D concentration. None of the patients had hypercalcaemia (i.e., calcium > 2.55 mmol/l) at baseline or after 2 months of treatment.

Serum concentrations of 25[OH]D, PTH, albumin, corrected calcium, phosphate and magnesium are shown in Table 2. Median 25[OH]D increased from 91 nmol/l before treatment to 101 nmol/l after 2 months of treatment (median change 6.0 nmol/l, IQR −0.7–25.0, $P = 0.001$). Median PTH increased from 1.6 to 2.0 pmol/l (median change 0.6, IQR −0.2–1.1, $P < 0.001$) and mean albumin increased from 26 to 35 g/l (mean change 9.0, 95%CI 7.1–11.0, $P < 0.001$).

Eighteen patients (22%) were sputum smear-positive even after 2 months of TB treatment. None had baseline vitamin D deficiency, while two (11%) had vitamin D insufficiency. Table 3 shows the 25[OH]D

Table 1 Patient characteristics ($N = 81$) at baseline and after 2 months of tuberculosis treatment

Characteristic	*n*	% (95%CI)
Age, years, median [IQR]	31 [26–41]	
Weight, kg, mean (SD)	52.5 (7.9)	
Male sex	64	79.0 (68.5–87.3)
HIV status		
Positive	8	9.9 (4.4–18.5)
Negative	72	88.9 (80.0–94.8)
Unknown	1	1.2 (0.03–6.7)
Sputum smear results at baseline		
Positive	74	91.4 (83.0–96.5)
Negative	1	1.2 (0.03–6.7)
Unknown	6	7.4 (2.8–15.4)
Sputum smear after 2 months of treatment		
Positive	18	22.2 (13.7–32.8)
Negative	55	67.9 (56.6–77.9)
Unknown	8	9.9 (4.4–18.5)
Vitamin D status at baseline*		
Normal	67	82.7 (72.7–90.2)
Insufficient	13	16.0 (8.8–25.9)
Deficient	1	1.2 (0.03–6.7)
Vitamin D status after 2 months		
Normal	67	82.7 (72.7–90.2)
Insufficient	14	17.3 (9.8–27.3)
Deficient	0	

*Normal vitamin D status, vitamin D insufficiency and deficiency were defined as serum 25[OH]D concentrations >75 nmol/l, 50–75 nmol/l and <50 nmol/l, respectively.
IQR = interquartile range; SD = standard deviation; HIV = human immunodeficiency virus.

Table 2 Serum indicators before and after 2 months of anti-tuberculosis treatment

Serum indicator	*n*	At baseline mean (SD) or median [IQR]	After 2 months mean (SD) or median [IQR]	Mean change (95%CI)	*P* value
Serum 25[OH]-D, nmol/l	81	91.0 [79.0–106.5]	101.0 [81.0–126.5]	6.0 (−7.0 – 25.0)	0.001
Parathyroid hormone, pmol/l	81	1.6 [1.0–2.0]	2.0 [1.5–2.7]	0.6 (−0.2–1.1)	<0.001
Albumin, g/l	48	25.8 (6.2)	34.8 (6.3)	9.0 (7.1–11.0)	<0.001
Corrected calcium, mmol/l*	48	1.9 [1.7–2.1]	2.2 [2.1–2.4]	0.3 (0.2–0.5)	<0.001
Phosphate, mmol/l	48	1.3 (0.3)	1.4 (0.2)	0.12 (0.04–0.19)	0.03
Magnesium, mmol/l	48	0.89 (0.11)	0.87 (0.06)	−0.02 (−0.05–0.01)	0.04

*Albumin-corrected calcium concentrations were calculated as: calcium + 0.02 × (40 − [albumin]).
SD = standard deviation; IQR = interquartile range; CI = confidence interval.

Table 3 Concentrations of 25-hydroxy-vitamin D for patients with a positive or negative sputum smear after 2 months

Sputum smear after 2 months	*n*	At baseline median [IQR]	After 2 months median [IQR]	Change median [IQR]	*P* value
Negative	55	90.5 [79.0–106.0]	103.0 [81.0–134.0]	8.0 [−6.0–30.0]	0.001
Positive	18	96.5 [86.8–109.8]	100.0 [73.8–115.8]	4 [−9.8–20.3]	0.35
Unknown	8	87.5 [74.3–105.8]	93.5 [78.0–99.8]	−4.5 [−12.0–16.8]	0.89

IQR = interquartile range.

concentrations at baseline and after 2 months divided by 2-month sputum smear result. There was no difference in baseline 25[OH]D concentration between patients who were sputum smear-negative (median 25[OH]D 90.5 nmol/l) and those who were sputum smear-positive (median 25[OH]D 96.5 nmol/l) after 2 months ($P = 0.40$).

Eight patients (9.9%) were HIV-positive. We found no evidence that HIV status was associated with serum 25[OH]D levels at baseline or after 2 months. Baseline median serum 25[OH]D concentrations were respectively 99.0 (IQR 89.3–116.5) and 90.0 nmol/l (IQR 79.0–105.5) in HIV-positive and HIV-negative patients ($P = 0.25$). After 2 months, serum 25[OH]D concentrations were respectively 89.5 (IQR 75.5–117.8) and 101.0 nmol/l (IQR 83.8–130.5) in HIV-positive and HIV-negative patients, ($P = 0.42$).

No correlation was found between vitamin D and calcium at baseline (Spearman's Rho correlation coefficient = 0.17, $P = 0.24$). The difference in vitamin D between baseline and 2 months was not correlated to the difference in corrected calcium between baseline and 2 months (Spearman's Rho correlation coefficient 0.20, $P = 0.17$).

DISCUSSION

This observational study in 81 hospitalised Tanzanian PTB patients showed that the median serum 25[OH]D concentration increased from 91 to 101 nmol/l during the first 2 months of TB treatment, and that none of the patients had vitamin D deficiency prior to TB treatment.

Little information is available about the effect of anti-tuberculosis drugs on vitamin D levels in TB patients. Previous studies from Brodie et al. in human volunteers showed that INH and RMP reduced serum 25[OH]D concentrations. These findings were confirmed in nine TB patients where 25[OH]D concentrations had decreased by respectively 20% and 50% after 1 and 6 months of TB treatment.[14] Our findings do not confirm this, but are in agreement with findings from a recent study from Guinea-Bissau, West Africa, where serum 25[OH]D concentrations increased during TB treatment in 178 patients who did not receive vitamin D supplements (from 78 nmol/l at baseline to 103 nmol/l after 2 months).[17]

Vitamin D levels can be influenced by several factors, such as dietary intake, sunlight exposure or medication.[23,24] There are several explanations for the increase in serum 25[OH]D concentrations in our study. Food and sunlight are important sources of vitamin D. The nutritional status of the patients probably improved during hospitalisation, as reflected by the increased albumin concentrations. The hospital menu included beans and (unfortified) milk almost daily, and meat and eggs several times per week. We do not, however, expect this menu to have increased the vitamin D status of the patients, as these foods naturally have a negligible vitamin D content.[23,24] The patients may have had increased sun exposure during hospitalisation, which could have increased their vitamin D concentrations. Activated macrophages and other immune cells can express 1-alfa-hydroxylase, the enzyme that converts 25[OH]D into $1,25[OH]_2D$, the active form of vitamin D.[1,9] In macrophages, 1α-hydroxylase is under the regulation of immune stimuli.[25,26] Down-regulation of these inflammatory stimuli, as occurs during TB treatment, could therefore have resulted in reduced hydroxylation of 25[OH]D and a consequent increase in serum 25[OH]D concentrations.

We were not able to measure $1,25[OH]_2D$ concentrations due to small serum volumes. Serum PTH concentrations increased from 1.7 ± 1.0 pmol/l at baseline to 2.2 ± 0.9 pmol/l after 2 months ($P < 0.001$). This could reflect decreased $1,25[OH]_2D$ concentrations, as the hydroxylation of 25[OH]D to $1,25[OH]_2D$ is regulated by PTH.

Our baseline serum 25[OH]D concentrations (median 91 nmol/l) are comparable to those found in Tanzanian PTB patients from a different study (mean 87 nmol/l).[27] In that study, however, 44% of the patients had vitamin D hypovitaminosis (25[OH]D < 75 nmol/l), compared to only 17% in our study (16% insufficiency and 1% deficiency). To our knowledge, Vitamin D concentrations from healthy Tanzanian adults were not available. Nevertheless, a recent study from healthy Guinea-Bissau adults had slightly higher 25[OH]D concentrations (mean 78.3 nmol/l, SD 22.6) compared to TB patients (mean 85.3 nmol/l, SD 34.8).[4]

Patients who had a positive sputum smear even after 2 months of treatment did not seem to have different 25[OH]D concentrations than patients who were smear-negative after 2 months, although the number of patients may have been too low for this subgroup analysis.

Our data did not show a correlation between baseline concentrations of 25[OH]D and corrected calcium, nor were there differences in 25[OH]D and corrected calcium concentrations between baseline and 2 months of TB treatment. The concentrations of 25[OH]D at baseline and after 2 months did not differ between HIV-positive and -negative patients, but again, this subgroup analysis may have been underpowered due to the low numbers.

In conclusion, vitamin D deficiency was rare in our study population and serum 25[OH]D concentrations increased during the first 2 months of TB treatment in hospitalised PTB patients in northern Tanzania. The optimal vitamin D status of patients treated for TB is unknown, but our data do not support the presence or development of poor vitamin D status during treatment.

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RÉSUMÉ

CONTEXTE : Les déficiences en vitamine D sont associées à une sensibilité à la tuberculose (TB) active dans de nombreux contextes. Les études in vitro et les études chez les volontaires humains ont montré que deux des médicaments antituberculeux de première ligne, l'isoniazide et la rifampicine, font baisser les concentrations de 25-hydroxy vitamine D (25[OH]D).

OBJECTIF : Etudier les modifications du statut en vitamine D au cours du traitement de la TB chez les patients tanzaniens hospitalisés pour TB pulmonaire (TBP).

SCHÉMA : Nous avons comparé les concentrations sériques de 25[OH]D chez 81 patients tanzaniens atteints de TBP, avant et après 2 mois de traitement.

RÉSULTATS : Les concentrations sériques médianes de 25[OH]D passent de 91 nmol/l au début à 101 nmol/l après 2 mois de traitement antituberculeux (augmentation médiane 6,0 nmol/l ; IQR −0,7–25,0 ; $P = 0{,}001$). Les concentrations sériques médianes de l'hormone parathyroïdienne sont passées de 01,6 à 2,0 pmol/l (augmentation médiane 0,46 ; IQR −0,2–1,1 ; $P < 0{,}001$).

CONCLUSION : Les concentrations sériques de 25[OH]D augmente au cours des 2 premiers mois du traitement de la TB chez 81 patients atteints de TBP au nord de la Tanzanie. Une amélioration de l'alimentation et une augmentation de l'exposition au soleil peuvent avoir contribué à l'augmentation des concentrations de 25[OH]D.

RESUMEN

MARCO DE REFERENCIA: La deficiencia de vitamina D se asocia con una vulnerabilidad a la tuberculosis (TB) activa en muchos entornos. Los estudios in vitro y en seres humanos voluntarios han demostrado que dos de los antituberculosos de primera línea, la isoniazida y la rifampicina, disminuyen las concentraciones de 25 hidroxivitamina D (25[OH]D).

OBJETIVO: Se buscó estudiar las modificaciones en las concentraciones de la vitamina D durante el tratamiento antituberculoso en pacientes hospitalizados por tuberculosis pulmonar (TBP) en Tanzania.

MÉTODO: Se comparó la concentración sérica de 25 [OH]D en 81 pacientes tuberculosos tanzanos antes y después de 2 meses de tratamiento.

RESULTADOS: La mediana de la concentración sérica de 25[OH]D aumentó de 91 nmol/l al inicio del tratamiento, a 101 nmol/l después de 2 meses de tratamiento antituberculoso (la mediana del aumento fue 6,0 nmol/l; IQR −0,7–25,0; $P = 0{,}001$). La mediana de la concentración sérica de hormona paratiroidea aumentó de 1,6 a 2,0 pmol/l (mediana del aumento 0,46; IQR −0,2–1,1; $P < 0{,}001$).

CONCLUSIÓN: La concentración sérica de 25[OH]D aumentó durante los 2 primeros meses del tratamiento antituberculoso en 81 pacientes con TBP en el norte de Tanzania. El incremento del aporte dietético y una mayor exposición a los rayos solares pueden haber contribuido al aumento de las concentraciones de 25[OH]D.