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Low prevalence of vitamin D deficiency in Ugandan HIV-infected patients with and without tuberculosis

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SUMMARY

OBJECTIVE: To examine whether hypovitaminosis D is a risk factor for the development of tuberculosis (TB) associated immune reconstitution inflammatory syndrome (IRIS).

METHODS: We measured serum 25-hydroxyvitamin D (25D) concentrations in four groups of patients at Mulago Hospital, Kampala, Uganda: 1) patients co-infected with TB and the human immunodeficiency virus (HIV) receiving anti-tuberculosis treatment (HIV+TB+; *n* = 92) who did and did not develop TB-IRIS after starting antiretroviral treatment (ART), 2) HIV-infected patients without TB (HIV+TB−; *n* = 20) starting ART, 3) non-HIV-infected individuals with TB (HIV−TB+; *n* = 27), and 4) those without TB (HIV−TB−; *n* = 23).

RESULTS: The prevalence of optimal 25D levels (>75 nmol/l) was as follows: 59% in HIV+TB+, 65% in HIV+TB−, 63% in HIV−TB+ and 35% in HIV−TB− patients. 25D concentrations decreased during the first 3 months of ART in HIV+TB+ individuals who developed IRIS (*P* = 0.005) and those who did not (*P* = 0.002), and in HIV+TB− individuals (*P* = 0.015); however, 25D concentration in patients who did or did not develop TB-IRIS did not differ.

CONCLUSION: The prevalence of optimal vitamin D status was relatively high in HIV-infected patients with and without TB living near the equator. No difference in 25D concentrations was observed between TB-IRIS and non-IRIS. However, 25D concentrations decreased during ART.

KEY WORDS: 25-hydroxyvitamin D; HAART; immune reconstitution

IT IS ESTIMATED that one billion people worldwide have insufficient vitamin D levels.[1] A high prevalence of vitamin D deficiency has been reported in African immigrants in industrialised countries,[2,3] in persons infected by the human immunodeficiency virus[4–7] and in patients with tuberculosis (TB),[8,9] but less is known about the vitamin D status of Africans living in Africa.

Humans acquire vitamin D mostly via the skin, through the conversion of 7-dehydrocholesterol by ultraviolet (UV) radiation, or from food such as oily fish and cod liver oil, fungi or vitamin D-supplemented food. To be hormonally active, vitamin D requires two successive hydroxylations: first in the liver (25-hydroxylation to produce 25-hydroxyvitamin D [25D]), then in the kidneys (1-α-hydroxylation to produce 1,25-dihydroxyvitamin D [1,25D]).[1] 1,25D can also be produced during inflammation at the site of infection by activated immune cells in response to inflammatory cytokines.[10] Although not the final form of vitamin D, 25D gives a more accurate approximation of an individual's vitamin D pool due to its longer half-life. Malabsorption, lower exposure to sunshine and darker skin pigmentation have been described as risk factors for low 25D levels.[1,11]

Several studies have associated low levels of 25D with TB,[8,12–15] and interestingly, historical treatment of TB relied on 25D supplementation in the form of cod liver oil or exposure to sun or UV light.[16]

Two recent studies have looked at the vitamin D status of black Africans with TB-HIV co-infection in Uganda (near the equator) and in Cape Town, South Africa (latitude 33°55′ south). In the first study conducted in Mbarara, Uganda, 62% of HIV-TB-co-infected individuals had 25D concentrations > 50 nmol/l, which was significantly lower than the levels in HIV-positive patients without TB (78%) or HIV-negative subjects without TB (80%).[17] Conversely, in Cape Town, the prevalence of 25D concentrations > 50 nmol/l was much lower, with 14% of

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HIV-TB-co-infected patients, 48% of HIV-positive patients without TB and 63% of HIV-negative subjects without TB.[18]

During immune reconstitution in HIV-infected individuals starting antiretroviral treatment (ART), 10–25% suffer worsening of TB.[19] This syndrome, termed TB-IRIS (immune reconstitution inflammatory syndrome), has been well described,[20] and risk factors for the development of TB-IRIS have been reported.[21,22] Although the pathogenesis of this syndrome is not well understood, it is thought to involve an exaggerated immune reaction against living TB organisms or residual TB antigens.[23]

In this study, we aimed to determine the vitamin D status of black Africans living near the equator, where exposure to sunshine is more regular. As Vitamin D has been shown to have immune-modulatory and antimycobacterial properties, we hypothesised that low vitamin D levels may favour the development of TB-IRIS.[24]

MATERIAL AND METHODS

Study population

In a prospective observational study conducted at the Mulago Hospital, Kampala, Uganda, four groups of patients were studied: 1) HIV-infected adults on treatment for active TB disease (described in[21,22]; HIV+TB+), 2) HIV-infected adults without active TB initiating ART (described in[25]; HIV+TB−), 3) non-HIV-infected adults on active TB treatment for <4 months (HIV−TB+), and 4) non-HIV-infected partners of HIV-positive patients without active TB (HIV−TB−) attending for routine HIV testing.

HIV-infected patients were followed for at least 6 months after initiation of non-nucleoside reverse transcriptase inhibitor (NNRTI) based ART. In these patients, plasma samples were collected before ART initiation and at 2 and 12 weeks of ART. Non-HIV-infected patients were seen only once by the study team for sample collection. All patients were dark-skinned.

Definitions

TB was defined according to the World Health Organization TB-HIV guidelines.[15] A person was considered not to have active TB in the absence of a relevant clinical history, no signs of TB on chest X-ray and sputum smear negativity (in the presence of cough).

TB-IRIS was defined according to the International Network for the Study of HIV-associated IRIS (INSHI) case definition.[16] HIV+TB+ non-IRIS controls were followed for a minimum of 3 months, and patients who developed signs and symptoms suggestive of IRIS or other forms of IRIS during the follow-up period were excluded.

Vitamin D status was defined as optimal (25D $\geqslant$ 75 nmol/l), suboptimal (25D 50–75 nmol/l), deficient (25D 25–50 nmol/l) and severely deficient (25D $<$ 25 nmol/l).

Vitamin D testing

Plasma samples were analysed by chemoluminescence using LIAISON® (DiaSorin, Stillwater, MN, USA) in the certified laboratory of the University Hospital of Antwerp. Quality control was performed by the vitamin D External Quality Assurance Survey (DEQAS, www.deqas.org).

Ethical considerations

The study was approved by the Makerere and Antwerp University Faculty of Medicine and Ethics Committees, the Mulago Hospital Research Committee and the Uganda National Council of Science and Technology. Informed consent was obtained from all study participants.

Statistical analysis

All statistical analyses were performed using Stata statistics software (version 10.2; Stata Corp, College Station, TX, USA) and GraphPad Prism (version 5; GraphPad Prism Inc, San Diego, CA, USA). Data were summarised by count and proportion (%) or median and interquartile range (IQR) for non-normally distributed variables. Normality was assessed using graphic methods. Differences between patient groups were assessed by Fisher's exact test for proportions and the Mann-Whitney *U*-test for medians. Decrease in 25D concentration was analysed using the Wilcoxon signed rank test for paired data.

RESULTS

Study participants

Baseline characteristics of the study participants are presented in Table 1. Thirty-nine patients from the HIV+TB+ cohort who developed TB-IRIS (median

Table 1 Characteristics of the four study populations

Variable	HIV+TB+ (n = 92) median [IQR]	HIV+TB− (n = 20) median [IQR]	HIV−TB+ (n = 27) median [IQR]	HIV−TB− (n = 23) median [IQR]
Male sex, n (%)*	52 (56)	12 (60)	14 (51.8)	8 (34.8)
Age, years†	34 [28–39]	34 [29–40]	25 [22–30]	37 [30–41]
CD4, cells/mm³	25.5 [14–74]	27 [17–69]	—	—

*No difference between groups (Fisher's exact test P = 0.274).
†HIV−TB− subjects older than HIV−TB+ subjects (Mann-Whitney test $P < 0.001$).
HIV = human immunodeficiency virus; TB = tuberculosis; + = positive; − = negative; IQR = interquartile range.

Table 2 Characteristics of the HIV+TB+ patients who developed TB-IRIS and non-IRIS controls

Variable	Total *n*	TB-IRIS (*n* = 39) *n* (%) or median [IQR]	Non-IRIS (*n* = 53) *n* (%) or median [IQR]	*P* value
Male sex	92	22 (56)	30 (56)	0.985
Age, years	92	32 [28–38]	35 [28–38]	0.467
CD4, cells/mm³	92	21 [11–70]	32 [17–79]	0.331
Sputum smear results	76			0.646
Negative		12 (40)	21 (46)	
Scanty or 1+		6 (20)	13 (28)	
2+		7 (23)	7 (15)	
3+		5 (17)	5 (11)	
Culture-positive	51	15 (83)	25 (76)	0.726
Type of TB	92			0.137
SS− PTB		7 (18)	19 (36)	
SS+ PTB		18 (46)	22 (41)	
EPTB ± PTB		14 (36)	12 (23)	
Time between TB treatment and ART, days, median [IQR]*	92	31 [24.5–58]	46 [30–60]	0.107

*Delay between the start of anti-TB treatment and commencement of ART.
HIV = human immunodeficiency virus; TB = tuberculosis; + = positive; IRIS = immune reconstitution inflammatory syndrome; IQR = interquartile range; SS = sputum smear; − = negative; PTB = pulmonary TB; EPTB = extra-pulmonary TB; ART = antiretroviral treatment.

time 14 days, IQR 11–18) were matched for age, sex and pre-ART CD4-T-cell count with 53 non-IRIS controls from the same group. No differences between groups were observed regarding sputum smear results, culture positivity, type of TB (pulmonary or extra-pulmonary) and time between anti-tuberculosis treatment and start of highly active ART (HAART; Table 2). The other groups included 20 HIV+TB−, 27 HIV−TB+ and 23 HIV−TB− persons. Sex distribution was not different among the groups, but HIV−TB− patients were older than HIV−TB+ patients ($P < 0.001$). 25D status was not associated with sex ($P = 0.128$) or age ($P = 0.246$) in the entire cohort. None of the patients were taking corticosteroids pre-ART, nor were corticosteroids prescribed during the study period.

Vitamin D status

Vitamin D status for the four patient groups did not differ significantly ($P = 0.138$, Table 3). No patient had severe vitamin D deficiency. Prevalence of optimal vitamin D levels (25D > 75 nmol/l) in the HIV+TB+, HIV+TB−, HIV−TB+ and HIV−TB− groups was respectively 59%, 65%, 63% and 35%. No significant difference was observed between the medians of the four groups studied (Figure 1).

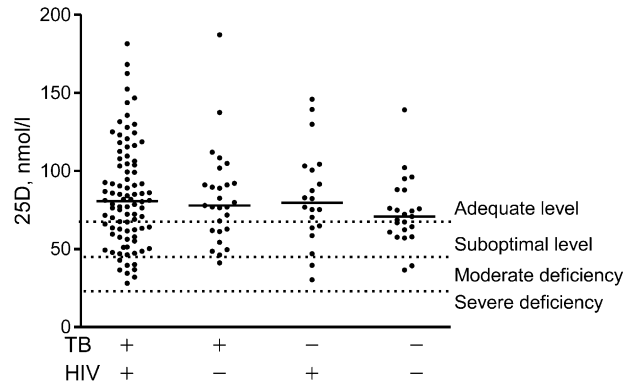

Figure 1 Baseline 25D concentrations in HIV+TB+ (*n* = 92), HIV+TB− (*n* = 20), HIV−TB+ (*n* = 27), and HIV−TB− (*n* = 23). No significant differences observed between medians by Mann-Whitney test. 25D = 25-hydroxyvitamin D; TB = tuberculosis; + = positive; − = negative; HIV = human immunodeficiency virus.

Difference in vitamin D concentrations in TB-IRIS vs. non-IRIS and evolution on ART

25D was not significantly different at any time point between patients who did or did not develop IRIS. Plasma 25D concentrations decreased during the first 3 months of ART in HIV+TB+ individuals who did (week 0: 81.4 nmol/l, IQR 62.1–117.5 vs. week 12: 64.5 nmol/l, IQR 47.0–92.7, $P = 0.005$) and who did not develop TB-IRIS (week 0: 79.5 nmol/l, IQR 55.6–99.2 vs. week 12: 72.1 nmol/l, IQR 55.5–83.6, $P = 0.002$), and in HIV+TB− individuals (week 0: 79.5 nmol/l, IQR 63.8–102.4 vs. week 12: 64.5 nmol/l, IQR 56.5–83.5, $P = 0.015$; Figure 2).

DISCUSSION

More than 50% of our patients had optimal vitamin D levels, irrespective of the presence of HIV infection or concomitant active TB. In HIV-infected patients, 25D levels decreased during the first 3 months of ART. We did not observe any difference in 25D levels between HIV+TB+ patients with and without TB-IRIS, either prior to or during the TB-IRIS episode.

Table 3 Vitamin D status of the four study populations

Vitamin D status	HIV+TB+ (*n* = 92) *n* (%)	HIV+TB− (*n* = 20) *n* (%)	HIV−TB+ (*n* = 27) *n* (%)	HIV−TB− (*n* = 23) *n* (%)
All, median [IQR]	81 [61–105]	79 [64–102]	78 [62–92]	71 [61–88]
Optimal (25D ⩾75 nmol/l)	54 (59)	13 (65)	17 (63)	8 (35)
Suboptimal (25D 50–75 nmol/l)	23 (25)	4 (20)	6 (22)	13 (56)
Deficient (25D 25–50 nmol/l)	15 (16)	3 (15)	4 (15)	2 (9)

HIV = human immunodeficiency virus; TB = tuberculosis; + = positive; − = negative; IQR = interquartile range; 25D = 25-hydroxyvitamin D.

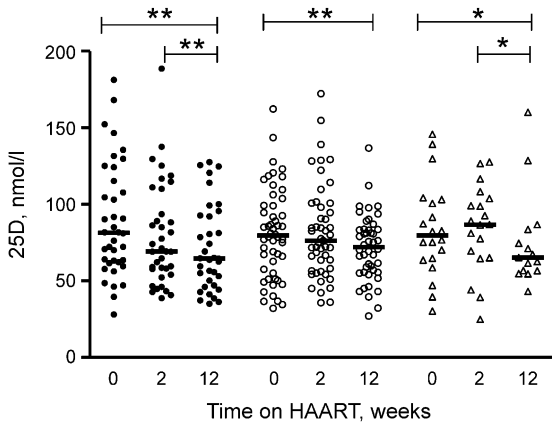

Figure 2 25D concentrations during follow-up in HIV-TB co-infected patients who did (●: $n_{baseline}$ = 38; n_{week2} = 37; n_{week12} = 35) or did not (○: $n_{baseline}$ = 52; n_{week2} = 49; n_{week12} = 46) develop TB-IRIS during follow-up and HIV-infected individuals without TB who did not develop TB-IRIS (△: $n_{baseline}$ = 20; n_{week2} = 19; n_{week12} = 15). Medians compared using the paired Wilcoxon sign rank test. $*P > 0.01 - P \leqslant 0.05$, $**P > 0.001 - P \leqslant 0.01$, $***P \leqslant 0.001$. 25D = 25-hydroxyvitamin D; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; TB = tuberculosis; IRIS = immune reconstitution inflammatory syndrome.

This is the largest study to date to describe vitamin D status in TB-IRIS cases matched with non-IRIS HIV+TB+ and HIV−TB+ controls. The vitamin D levels of the participants in our study are comparable to those reported by the Mbarara study in Uganda,[17] but are much higher than in a similar cohort of black African subjects with HIV and/or TB in Cape Town, South Africa.[18] This difference cannot be explained by the different techniques used for vitamin D testing, as they have been shown to be comparable,[26] but most probably by the difference in latitude between the two settings, and consequently the difference in solar UV exposure. It might be that TB is an important risk factor for vitamin D deficiency in patients with pre-existing low vitamin D at TB diagnosis. If vitamin D levels are low, a small difference in vitamin D intake/production could have more important consequences on the vitamin D pool in those patients.

As vitamin D has been reported to have antimycobacterial properties,[27] we investigated the relationship between vitamin D and the occurrence of TB-IRIS. Despite the high prevalence of optimal vitamin D levels in HIV patients at the start of ART, the incidence of TB-IRIS in our HIV+TB+ cohort[22] was not lower than those reported in a meta-analysis on IRIS.[19] Our study confirms previous findings that 25D levels at the start of ART are not different between patients who developed TB-IRIS and those who did not, in settings with both low[17] and high (manuscript submitted) prevalence of vitamin D deficiency. Our study therefore does not support the hypothesis that vitamin D deficiency predisposes to TB-IRIS.

Despite its antimycobacterial properties in vitro,[28,29] vitamin D action in vivo on clinical resolution of TB seems to be limited.[29] In HIV-positive patients, the action of vitamin D may be less prominent, as it may require a functional, competent immune system to fight *Mycobacterium tuberculosis* infection. It is known that 25D needs to be locally converted to active vitamin D by activated immune cells.[10] Furthermore, the interaction between ART and anti-tuberculosis drugs with the enzymes of the vitamin D metabolism pathway[30] might interfere with the production of sufficient levels of local 1,25D from circulating 25D. As we have previously shown in HIV-infected patients in Belgium,[31] and in HIV+TB+ patients in Cape Town, South Africa (manuscript submitted), 25D plasma levels decreased during the first months of ART. This reduction in 25D during ART could result from a drug interaction with the vitamin D metabolism enzymes, as NNRTI-based ART has often been associated with lower or decreased 25D levels in cross-sectional and prospective studies.[27,31–33] Rifampicin and isoniazid could equally reduce vitamin D levels, regardless of HIV status.[34]

In conclusion, vitamin D supplementation might not prevent the development of TB-IRIS, but could be considered in patients on ART and/or anti-tuberculosis treatment to maintain optimal levels and reduce acquired immune-deficiency syndrome related mortality.[35] The mechanism of interaction of ART with vitamin D metabolism enzymes and its consequences for patients' health should be further investigated.

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RÉSUMÉ

OBJECTIF : Examiner si l'hypovitaminose D pourrait être un facteur de risque de développement du syndrome inflammatoire de reconstitution immunitaire (IRIS) lié à la tuberculose (TB).

MÉTHODES : Nous avons mesuré les concentrations de 25-hydroxyvitamine D (25D) dans quatre groupes de patients à l'Hôpital Mulago à Kampala, Ouganda : les patients co-infectés par le virus de l'immunodéficience humaine (VIH) et la TB sous traitement TB (VIH+TB+ ; n = 92) qui avaient ou non développé un IRIS-TB après la mise en route du traitement antirétroviral (ART), ainsi que les patients infectés par le VIH sans TB (VIH+TB− ; n = 20) mis sous ART et les individus non-infectés par le VIH mais atteints de TB (VIH−TB+ ; n = 27) ou sans TB (VIH−TB− ; n = 23).

RÉSULTATS : La prévalence des niveaux optimaux de 25D (>75 nmol/l) était de 59% chez les patients VIH+TB+, 65% chez les patients VIH+TB−, 63% chez les patients VIH−TB+ et 35% chez les patients VIH−TB−. La concentration de 25D diminue au cours des 3 premiers mois de l'ART chez les individus VIH+TB+ qui ont développé l'IRIS (P = 0,005) ou non (P = 0,002), ainsi que chez les individus VIH+TB− (P = 0,015), mais il n'y avait pas de différence dans les concentrations de 25D entre les patients qui ont ou qui n'ont pas développé le IRIS-TB.

CONCLUSION : La prévalence d'un statut optimal en vitamine D était relativement élevée chez les patients infectés par le VIH avec ou sans TB et vivant près de l'equateur. On n'a pas observé de différence de concentration du 25D entre les TB-IRIS et les non-IRIS. Toutefois, la concentration de 25D a diminué pendant l'ART.

RESUMEN

OBJETIVO: Proponer la hipótesis que la hipovitaminosis D podría constituir un factor de riesgo de aparición del síndrome inflamatorio de recuperación inmunitaria (IRIS) asociado con la tuberculosis (TB).

MÉTODOS: En el Hospital Mulago de Kampala en Uganda se midió la concentración sérica de 25-hidroxivitamina D (25D) en los siguientes cuatro grupos de pacientes: los pacientes coinfectados por el virus de la inmunodeficiencia humana (VIH) y la TB en curso de tratamiento antituberculoso (VIH+TB+; n = 92) que presentaron y no presentaron el IRIS después del comienzo del tratamiento antirretrovírico (ART); los pacientes infectados por el VIH sin TB (VIH+TB−; n = 20) que comenzaban el ART; los pacientes tuberculosos sin infección por el VIH (VIH−TB+; n = 27) y los pacientes sin TB ni infección por el VIH (VIH−TB−; n = 23).

RESULTADOS: La prevalencia de concentraciones óptimas de vitamina 25D (>75 nmol/l) fue 59% en el grupo VIH+TB+, 65% en el grupo VIH+TB−, 63% en los pacientes VIH−TB+ y 35% en el grupo de pacientes VIH−TB−. La concentración de 25D disminuyó durante los primeros 3 meses de ART en los pacientes VIH+TB+ que presentaron el IRIS (P = 0,005) y en los pacientes que no lo presentaron (P = 0,002) y también en los pacientes VIH+TB− (P = 0,015). No se observó ninguna diferencia entre los pacientes que presentaron IRIS asociado a la TB y quienes no lo presentaron.

CONCLUSIÓN: La prevalencia de una concentración óptima de vitamina D fue relativamente alta en los pacientes infectados por el VIH que padecían o no TB y vivían cerca al ecuador. No se observó una diferencia en la concentración de 25D en los pacientes tuberculosos con o sin el IRIS. Sin embargo, la concentración de 25D disminuyó durante el ART.