

Vitamin D deficiency is associated with tuberculosis infection among household contacts in Ulaanbaatar, Mongolia

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SUMMARY

BACKGROUND: Vitamin D deficiency (VDD) is a known risk factor for tuberculous infection. We investigated if VDD is a risk factor for tuberculous infection among the household contacts (HHCs) of patients with tuberculosis (TB) in Mongolia.

MATERIALS AND METHOD: All HHCs of TB patients diagnosed in Khan-Uul District, Mongolia, were enrolled. The serum level of 25-hydroxyvitamin D [25(OH)D] was detected and TB infection determined using QuantiFERON-TB Gold Plus (QFT-Plus). A tuberculin skin test (TST) reading >10 mm was considered to be positive. Epidemiological and bacteriological data were collected from routine surveillance of the National Tuberculosis Programme.

RESULTS: Among study participants, 48.2% (135/285) were QFT-Plus-positive. Of QFT-positive HHCs, 77.0%

(104/135) were TST-positive and the overall concordance of tests was low (κ 0.374, $P < 0.001$). A low serum level of 25(OH)D was an independent predictor for QFT-Plus positivity ($P < 0.001$). CD8⁺ T-cell stimulation measured by QFT-Plus had borderline association with the serum level of 25(OH)D ($P = 0.089$).

CONCLUSION: We showed a high rate of TB infection among HHCs in Mongolia. QFT-Plus could decrease the number of people requiring TB preventive treatment, in addition to aiding detection of new TB infection. A low serum level of vitamin D was an independent predictor of TB infection, but not a predictor of stimulation of CD8⁺ T cells.

KEY WORDS: VDD; latent tuberculous infection; CD8⁺ T-cell stimulation; tuberculin skin test

VITAMIN D DEFICIENCY (VDD) is a known risk factor for TB infection and progression to TB.^{1,2} In particular, TB household contacts (HHCs) with a low serum level of vitamin D are at a high risk of acquiring TB infection.³

Studies conducted in Mongolia by Ganmaa et al. have shown a high prevalence of VDD among reproductive-aged women and school children.⁴ Ganmaa et al. have also shown that children who had taken VDD supplementation had lower tuberculin skin test (TST) conversion than that in the placebo group.^{5,6}

The TST is an inexpensive and rapid way to detect latent tuberculous infection (LTBI). However, the TST can cross-react with the bacille Calmette-Guérin (BCG) vaccine and non-tuberculous mycobacteria, which can lead to false-positive results.^{7,8} Thus, a

more specific test, the interferon-gamma release assay (IGRA), which overcomes the disadvantages of the TST, has been developed.⁹

The World Health Organization has endorsed two IGRAs for LTBI detection: QuantiFERON-TB Gold In-Tube (QFT-GIT; Qiagen, Hilden, Germany) and T-SPOT.TB (Oxford Immunotec, Abingdon, UK).¹ The next generation of QFT-GIT, QuantiFERON-TB Gold Plus (QFT-Plus; Qiagen), has been developed to be equally sensitive and specific as the WHO-approved tests, but can also detect the TB antigen-stimulated CD8⁺ T-cell response.^{9,10} The CD8⁺ T-cell response in QFT-Plus has been found to be highly increased in people with recent LTBI, a finding that could be used to predict recent infection and progression to TB.^{11,12}

Mongolia provides routine BCG vaccination to

each new-born. We used QFT-Plus as a measure to detect TB infection among the HHCs of TB patients. Here, we aimed to explore the association between the serum level of 25-hydroxyvitamin D [25(OH)D] and TB infection in a VDD-prevalent setting.

MATERIALS AND METHODS

Study population

A cross-sectional study was conducted in Khan-Uul District, Mongolia, which has urban and semi-urban populations, and whose inhabitants account for ~10% of the capital city Ulaanbaatar (population of 1.4 million). We recruited the HHCs of TB patients diagnosed between January and August 2017.

We defined a 'HHC' as anyone who lived with the TB patient ≥ 3 months before the diagnosis in the same household and or in the same fenced area at a different house. HHCs known to have TB or who were being treated for TB were excluded from our study. The epidemiological and clinical data of HHCs and TB patients were collected from routine surveillance data of the National Tuberculosis Programme. Also, socio-economic and behavioural data were collected.

Ethical approval was obtained from the Mongolian National University of Medical Sciences (Ulaanbaatar, Mongolia). All study participants provided written informed consent.

Laboratory tests

The peripheral blood of HHCs was collected in QuantiFERON-TB Gold Plus tubes. All tubes were mixed and incubated immediately at 37°C and transported to Global Lab (Mongolian Health Initiative, Ulaanbaatar, Mongolia) within 4 h. After continuous incubation for up to 16–24 h, serum was separated and IGRA was carried out according to manufacturer instructions.⁹ A participant with a borderline result was excluded from the study. QFT-Plus has two test tubes, TB1 and TB2, that each estimate the number of CD4⁺ and CD4⁺/CD8⁺ T-cells. CD8⁺ T-cell stimulation was estimated from QFT-Plus, and considered to be increased if the difference between the TB2 tube and TB1 tube was >0.6 IU/ml.¹²

The TST of study participants was carried out by a specially trained nurse. The result was read within 72 h by this nurse. A reaction of ≥ 10 mm was considered to be positive according to a decree (A306) set by the Ministry of Health of Mongolia in 2017.¹³ The cut-off value of the TST was set according to a Mongolian ministerial order.¹⁴

The 25(OH)D assay was carried out in frozen serum (-80°C) at a Vitamin D External Quality Assessment Scheme (DEQAS) assured Global Lab using a MiniVidas[™] compact automated machine (BioMérieux, Marcy l'Etoile, France). A level of

vitamin D of 30–100 ng/ml was considered to be 'sufficient', 20–30 ng/ml to be 'insufficient' and <20 ng/ml to be 'deficient'.^{15,16}

Statistical analysis

The demographic characteristics of HHCs were explored using the χ^2 test. $P < 0.05$ was considered statistically significant. STATA v12 (STATA Corporation, College Station, TX, USA) was used to calculate Cohen's κ coefficient to ascertain the agreement between QFT-Plus and TST. Multivariable logistic regression was used to evaluate independent associations between 1) the primary exposure (serum 25(OH)D concentration) and IGRA positivity, and 2) 25(OH)D and CD8⁺ T-cell stimulation. For each outcome, four progressively complex models were run to evaluate other potential independent predictors and potential confounders. These four models evaluated the potential modification of effects adjusted and unadjusted by age and sex. They also evaluated the potential influence of age, body mass index (BMI), as well as socio-economic, behavioural, and clinical characteristics (Supplementary Table S1A and B).

In the descriptive analysis, 34 (12.6%) of 25(OH)D measurements fell below the limit of detection (8.1 ng/ml) and were imputed at 8.1 ng/ml in the regression analysis. The distribution of 25(OH)D was approximately visually normal except for the resultant peak at the limit of detection (Supplementary Figure S1). To account for the potential non-normality of residuals in the regression analysis, two sensitivity analyses were conducted after 1) applying a natural logarithm transformation to 25(OH)D, and 2) excluding observations below the limit of detection. Neither analysis produced materially different parameter estimates or associated P values, so the results of these analyses have been omitted for simplicity. Models were also run after excluding the highest value of 25(OH)D (43.4 ng/ml), which also did not affect the results.

RESULTS

Characteristics of the study population

Two hundred and eighty-five eligible participants had QFT-Plus data. Of these 285 participants, TST data were available for 280 (98.2%) and vitamin D data were available for 268 (94.4%). Of the participants, 48.2% (135/280) were QFT-Plus-positive or latently infected with TB (Table). Although no significant difference was seen in males or females with regard to QFT-Plus positivity, different age groups had a different prevalence ($P = 0.001$). In particular, the prevalence of QFT-Plus-positivity peaked in the 30–44 years group (47/69, 68.1%), followed by the 45–59 years group (30/54, 55.6%).

A higher number of QFT-Plus-negative HHCs had

Table Characteristics of the QFT-Plus-positive household contacts of TB patients

Characteristics	QFT-Plus result		Total n (%)	P value
	Positive n (%)	Negative n (%)		
HHC sex (n = 285)*				0.3
All	137 (48.0)	148 (52.0)	285 (100)	
Female	69 (45.7)	82 (54.3)	151 (100)	
HHC age group (n = 285)*, years				0.001
<15	30 (29.7)	71 (70.3)	101 (100)	
15–29	23 (48.9)	24 (51.1)	47 (100)	
30–44	47 (68.1)	22 (31.9)	69 (100)	
45–59	30 (55.6)	24 (44.4)	54 (100)	
≥60	7 (50)	7 (50)	14 (100)	
HHC vitamin D status (n = 269)*				0.058
Sufficient	3 (20.0)	12 (80.0)	15 (100)	
Insufficient	33 (44.0)	42 (56.0)	75 (100)	
Deficient	91 (50.8)	88 (49.2)	179 (100)	

* HHCs grouped by sex, age group, and vitamin D status.

HHC = household contact; MDR-TB = multidrug-resistant TB; QFT-Plus = QuantiFERON-TB Gold Plus.

a sufficient serum level of 25(OH)D as compared with TB-infected people (12/15, 80.0% vs. 3/15, 20.0%; $P = 0.058$). In addition, more HHCs were infected with TB when the TB patient was diagnosed as having smear-positive TB as compared with smear-negative patients (57/96, 59.4% vs. 39/96, 40.6%; $P = 0.002$). However, the drug susceptibility test of the TB index case had no effect on the prevalence of TB infection (44.1% vs. 45.2%, $P = 0.1$). The characteristics of TST-positive contacts are shown in Supplementary Table S2.

QuantiFERON-TB-Plus has low concordance with the tuberculin skin test

Poor concordance of QFT-Plus and TST (κ 0.374, 95% confidence interval (CI) 0.21–0.40), $P < 0.001$ with agreement of 68.9% (193/280) was observed (Supplementary Table S3). Of the discordant cases, TST-positive and QFT-Plus-negative cases were the most numerous ($n = 56$, 20.0%), followed by TST-negative and QFT-Plus-positive ($n = 31$, 11.1%) cases. Discordance between QFT-Plus-positivity and TST-positivity varied across age groups; the prevalence of positivity differed up to 12.8% in those aged ≤ 9 years and 9–20 years, and 8.6% in those aged ≥ 48 years (Supplementary Figure S2).

Interestingly, 22.6% (31/137) of QFT-Plus-positive participants had increased levels of CD8⁺ T-cells (TB2 – TB1 cut-off > 0.6 IU/ml) and none of these participants had a sufficient serum level of 25(OH)D. Of those 31 people with increased levels of CD8⁺ T-cells, 93.5% of HHCs were TST-positive, thereby indicating the highest concordance with the QFT-Plus result.

The serum level of 25-hydroxyvitamin D is an independent predictor for latent tuberculous infection
Of all HHCs, 94.4% (254/269) had insufficient or

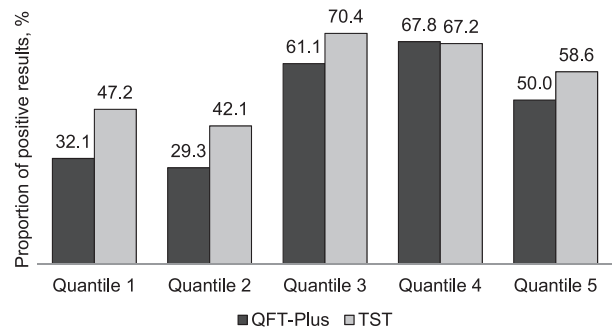


Figure 1 Positive rate of QFT-Plus and TST results by household contacts' age. *Quantile 1 = ≤ 9 years; quantile 2 = 9–20 years; quantile 3 = 21–33 years; quantile 4 = 34–47 years; quantile 5 = ≥ 48 years. QFT-Plus = QuantiFERON®-TB Gold Plus; TST = tuberculin skin test.

deficient 25(OH)D levels, of which 70.5% (179/254) had VDD. Regression analysis showed the serum 25(OH)D concentration to be negatively associated with QFT-Plus positivity (Figure 1A) after adjustment for age, sex, BMI as well as socio-economic, behavioural, and clinical characteristics (odds ratio [OR] 0.92, 95% CI 0.88–0.97). Other independent predictors in fully adjusted models were age quintiles three (21–33 years, OR 7.7, 95% CI 1.5–40.7), four (34–47 years, OR 13.7, 95% CI 2.3–82.0) and female sex (OR 0.50, 95% CI 0.25–0.97). BMI was significantly predictive of QFT-Plus positivity in age- and sex-adjusted models, but this association was not robust to further adjustment for socio-economic and behavioural factors. The serum level of 25(OH)D showed a borderline negative association with levels of CD8⁺ T cells in unadjusted (OR 0.95, $P = 0.089$) and fully adjusted models (OR 0.94, $P = 0.087$) (Figure 1B). Regression models did not indicate significant modification of effects by age or sex (Supplementary Table S1A and B).

DISCUSSION

Similar to other vitamin D studies conducted in reproductive-aged women and school children in Mongolia, the prevalence of VDD was extremely high among HHCs of people with TB. Also, we showed that a low serum level of 25(OH)D is an independent predictor of TB infection among HHCs in Mongolia.

A cohort study by Nnoaham et al. showed that an increase in the serum level of 25(OH)D of 1 ng/ml decreased the TB incidence by 6%.^{17,18} In our study, BMI was identified to be a risk factor for TB infection. A systematic review showed that, independent of high and low TB settings, low BMI was strongly related to TB infection, and that an increase in BMI of 1 unit reduced the prevalence of TB infection by 13.8%.¹⁹ Conversely, a high serum level of vitamin D coupled with high BMI could be protective factors against LTBI. However, in our

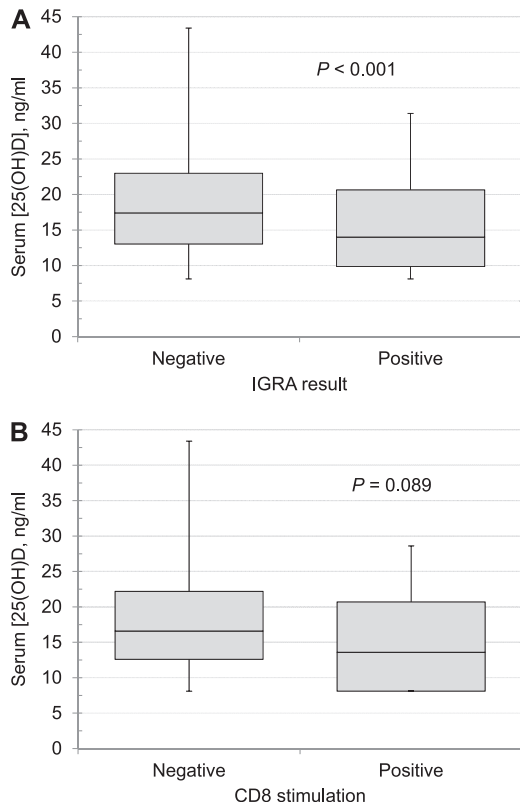


Figure 2 Serum level of 25(OH)D is an independent predictive factor for LTBI as measured using QFT-Plus but not for stimulation of CD8⁺ T cells. 25(OH)D = 25-hydroxyvitamin D; LTBI = latent tuberculosis infection; IGRA = interferon gamma release assay.

study, the serum level of 25(OH)D and BMI were not significant predictors for levels of CD8⁺ T-cells.

We sought to compare TST and QFT-Plus with regard to detection of TB infection among paediatric HHCs and adult HHCs. He found a high prevalence of TB infection regardless of the assay used among HHCs in Mongolia. Also, the rate of QFT-Plus positivity increased with age, but people aged 30–59 years were affected more by TB than the other age groups tested. A study conducted in another setting of high TB prevalence, Brazil, showed a similarly high rate of IGRA positivity among HHCs.²⁰ However, the rate was 2–4 times lower in a country with a low TB incidence, such as Japan.²¹ Another meta-analysis detected a high rate of LTBI and active TB cases in low-income countries.²² We showed a low concordance of the TST and QFT-Plus, data that are consistent with the findings of a meta-analysis carried out in 2010 by Diel et al.²³ The highest rate of discordance of the tests was observed in the young age group. This finding could have been due to a cross-reaction with the BCG vaccine, or due to the immature immune system of the children.¹³ Unlike our result, a study in South Korea showed a discrepancy between IGRA and TST in people aged 30–39 years and ≥ 60 years, but not in children or

young adults.²⁴ One meta-analysis suggested that IGRA had higher specificity than TST, and was more likely to rule out uninfected people.²³ Studies by Higuchi et al. and Emmanuel et al. showed that the use of IGRA decreased the number of TB-infected people who received TB preventive treatment.^{25,26} In our study, higher number of HHCs were infected with TB when index case was diagnosed with sputum smear-positive tuberculosis, as has been shown in the study conducted in the United States.²⁷

One quarter of study participants with QFT-Plus positivity had increased numbers of CD8⁺ T-cells. QFT-Plus has two test tubes, TB1 and TB2, that each estimate the number of CD4⁺ and CD4⁺/CD8⁺ T-cells.³ A recent study showed that QFT-Plus-positive results and CD8⁺ T-cell responses had a stronger correlation to TB exposure risk than QFT-GIT, thereby suggesting that the stimulation of CD8⁺ T-cells could be a determinant of recent TB infection.²⁸ A flow cytometry study showed that an increased number of CD8⁺ T-cells in the TB2 tube was correlated with active TB, whereas the number of CD8⁺ T-cells in the TB1 tube was high in active and latent TB.²⁹ As a potential marker of new infection which carries a higher risk of disease progression, our data for CD8⁺ T-cells suggest that $\geq 25\%$ of HHCs may have new TB infection, and should be prioritised for treatment.

A recent study among Mongolian schoolchildren suggested household pulmonary TB and VDD are risks for TB infection.³⁰ Despite the difference in the study population, our study among the HHCs of TB patients also showed that a low serum level of 25(OH)D was a predictor of TB infection. The 25(OH)D in serum is catalysed to 1,25(OH)₂D₃, which subsequently induces expression of vitamin D receptors (VDRs). A downstream pathway of VDRs induces production of cathelicidins, which have critical roles in mammalian innate immune defence against invasive bacterial infection.³¹ Studies have shown a decreased level of vitamin D among LTBI and TB patients, and that supplementation with vitamin D in TB patients shows early sputum smear conversion and improved radiological changes.^{32,33}

In conclusion, we showed a high rate of TB infection among HHCs in Mongolia. QFT-Plus could decrease the number of people requiring TB preventive treatment, in addition to aiding detection of new TB infection. A low serum level of vitamin D was an independent predictor of TB infection, but not a predictor of stimulation of CD8⁺ T-cells.

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Conflicts of interest: none declared.

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R É S U M É

CONTEXTE : La carence en vitamine D (VDD) est un facteur de risque connu d'infection tuberculeuse (TB). L'étude actuelle a recherché si la VDD était un facteur de risque d'infection TB parmi les contacts domiciliaires (HHC) de patients TB en Mongolie.

MATÉRIEL et MÉTHODE : Tous les HHC des patients TB diagnostiqués à Ulaanbaatar, Mongolie, ont été enrôlés dans l'étude. Le taux de 25-hydroxyvitamine D [25(OH)D] sérique des participants a été mesuré et la présence d'une infection TB a été déterminée par QuantiFERON®-TB Gold Plus (QFT-Plus). La réaction d'un test cutané à la tuberculine (TCT) >10 mm a été considérée comme positive. Les données épidémiologiques et bactériologiques ont été recueillies grâce à la surveillance de routine du Programme National Tuberculose.

RÉSULTATS : Parmi les participants de l'étude, 48,2% (135/285) ont été positifs au QFT-Plus. Parmi eux, 77,0% (104/135) ont eu un TCT positif et la concordance d'ensemble des tests a été faible (κ 0,374, $P < 0,001$). Une faible concentration sérique de 25(OH)D a été un facteur de risque indépendant de positivité de QFT-Plus ($P < 0,001$). La stimulation des CD8+ mesurée par QFT-Plus a eu une association limite avec le taux de 25(OH)D sérique ($P = 0,089$).

CONCLUSION : Le taux d'infection tuberculeuse est élevé quel que soit le test utilisé parmi les HHC de patients TB en Mongolie. Un taux sérique bas de vitamine D prédit l'infection tuberculeuse parmi les contacts domiciliaires des patients TB et c'est pourquoi nous recommandons la détection et le traitement de la carence en vitamine D dans ce groupe.

RESUMEN

MARCO DE REFERENCIA: La deficiencia de vitamina D es un factor de riesgo reconocido de contraer la infección tuberculosa. En el presente estudio se investigó si esta deficiencia representa un riesgo de infección tuberculosa en los contactos domiciliarios (HHC) de los pacientes con tuberculosis (TB) en Mongolia.

PACIENTES, MATERIAL y MÉTODOS: Se incluyeron en el estudio todos los HHC de pacientes con TB diagnosticados en Ulan-Bator, en Mongolia. Se investigó en los participantes la concentración sérica de 25-hidroxivitamina D [25(OH)D] y se determinó la presencia de infección tuberculosa mediante la prueba QuantiFERON-TB Gold Plus (QFT-Plus). Una reacción tuberculínica >10 mm se consideró positiva. Los datos epidemiológicos y bacteriológicos se extrajeron de la vigilancia corriente del Programa Nacional de Tuberculosis.

RESULTADOS: De los participantes, el 48,2% (135/

285) obtuvo un resultado positivo de la prueba QFT-Plus. En los contactos de las personas con QFT positiva, el 77,0% (104/135) tuvo una prueba tuberculínica positiva y la concordancia global de las pruebas fue baja (κ 0,374; $P < 0,001$). Una baja concentración de 25(OH)D sérica fue un factor pronóstico independiente de positividad de la prueba QFT-Plus ($P < 0,001$). La estimulación de linfocitos CD8+, que se midió mediante la prueba QFT-Plus, exhibió una asociación marginal con la concentración de 25(OH)D sérica ($P = 0,089$).

CONCLUSIÓN: En Mongolia, la tasa de infección tuberculosa en los HHC es alta, sea cual fuere la prueba de detección utilizada. Una baja concentración sérica de vitamina D es un factor pronóstico de infección tuberculosa en los contactos de pacientes con TB y por esta razón se recomienda la detección y el tratamiento de la deficiencia de vitamina D en este grupo de personas.