Basic vitamin D concentration in multi-drug resistant tuberculosis patients in Latvia

Sabīne Upmale1,2, Rihards Engels3,4, Liga Kukša3,5

1Department of Internal Medicine, Riga East Clinical University Hospital, Riga, Latvia
2Faculty of Continuing Education, Riga Stradins University, Riga, Latvia
3Riga Stradins University, Riga, Latvia
4Department of Orthopedic Surgery, Hospital of Traumatology and Orthopedics, Riga, Latvia
5Department of Multidrug Resistant Tuberculosis, Centre of Tuberculosis and Lung Diseases, Riga East Clinical University Hospital, Riga, Latvia

Abstract

Purpose: The primary goal of this study was to determine the basic concentration of vitamin D in patients with multidrug-resistant tuberculosis (MDR-TB) and its correlation with gender, age, and comorbidities.

Methods: This retrospective observational study comprised all adult patients diagnosed with active MDR-TB in Latvia during the period between January 2014 and December 2016. We analyzed patients’ anthropometric data, serum vitamin D concentrations, comorbidities, and laboratory findings at the time of diagnosis.

Results: Out of a total of 170 patients, 75.3% were male with a median age of 47 years. Vitamin D concentration was determined in 75 cases (44.1%). Out of them, 78.67% had vitamin D deficiency and 20% had insufficiency, while only 1.33% had optimal vitamin D concentration. The median concentration of vitamin D was 14.1 ng/ml (interquartile range 10.3–19.4). There was no statistically significant relationship between gender (F = 3.638, P = 0.060), age (r = −0.179, P = 0.124), or comorbidities (F = 0.677, P = 0.691) and vitamin D concentration.

Conclusion: Almost all MDR-TB patients have insufficient or deficient vitamin D concentrations. Therefore, it is recommended to assess vitamin D concentration in all MDR-TB patients to start proper substitution therapy.

Key words: Multidrug-resistant tuberculosis; vitamin D deficiency; outcome
1. Introduction

Tuberculosis (TB) is one of the leading causes of death worldwide, and thus, represents a global public health problem [1]. In the year 2015, a total of 10.4 million people were diagnosed with TB while there were more than 1.8 million deaths from the disease. It also represents one of the main causes of death among human immunodeficiency virus (HIV) positive patients [2]. More than 95% of deaths from TB come from low- and middle-income countries [3]. Fortunately, the incidence of TB decreases by approximately 1.5% per year [2]. Nevertheless, the target is to decrease its incidence by 4-5% yearly to reach the 2020 milestones of the “end TB strategy” [4]. In addition, stopping the TB epidemic by the year 2030 is one of the health targets of the newly adopted sustainable development goals [5]. In 2015, the highest incidence of TB was in Asia (61% of new cases) followed by Africa (26% of new cases). In Latvia, the number of newly diagnosed TB patients was 637 (31.8 per 100 000) in the year 2014, 621 (31.3 per 100 000) in 2015, and 560 (28.4 per 100 000) in 2016 [6].

Multidrug-resistant tuberculosis (MDR-TB) is caused by microorganisms that cause the clinical form of the disease and are unresponsive to at least 2 first-line anti-TB drugs: Isoniazid and rifampicin [7]. It can be treated using second-line drugs. Nevertheless, this treatment is more expensive, toxic, and even more extensive: It might last up to 2 years [7]. About 480,000 people worldwide developed MDR-TB in 2015 [2]. MDR-TB is mostly seen in China, India, and the Russian Federation [2]. In Latvia, there were 63 MDR-TB cases in 2014, 56 in 2015, and 46 in the year 2016 [8].

As drug-resistance is becoming more common, several adjunctive therapy methods have been explored. It has been noticed that patients with TB have lower concentrations of vitamin D (25(OH)D) when compared to the general population [9]. Moreover, people with lower vitamin D concentrations have a 5-fold increased risk for the progression of active TB [10]. Therefore, the immunomodulating effects of vitamin D have been widely explored [11]. Several studies have investigated the effectiveness of vitamin D supplementation in patients with active TB, MDR-TB, and the effect of vitamin D receptor (VDR) polymorphism on the disease course [12]. Vitamin D deficiency is common in the Latvian population [13], and since available data show a strong link between vitamin D deficiency and TB, the aim of this study was to assess the vitamin D (25(OH)D) concentrations in Latvian patients with MDR-TB.

2. Materials and Methods

2.1. Study design and subjects

This retrospective observational study was carried out in Riga, Latvia, and included all patients that were diagnosed with MDR-TB infection between January 2014 and December 2016. The following data were collected for each patient: Gender, age, and comorbidities (HIV, hepatitis C virus [HCV] infection, HIV, and HCV co-infection, diabetes type 1 and type 2, chronic kidney disease), total 25(OH)D concentration, thyroid-stimulating hormone (TSH), free triiodothyronine, free thyroxine (fT4), calcium (Ca), sodium (Na), potassium (K), C-reactive protein (CRP), glomerulofiltration rate (GFR), fasting plasma glucose, chest X-ray, chest computed tomography, sputum smear results, GeneExpert nucleic acid amplification test results, and culture results (Bactec blood culture system, Lowenstein-Jensen medium). The study was approved by the Ethical Committees of the Center for Tuberculosis and Lung Diseases.

TB was diagnosed according to standard procedure when there was acid-fast bacilli (AFB) seen on sputum smears, and Mycobacterium tuberculosis was isolated by culture. AFB was assessed using either fluorescence microscopy (auramine-rhodamine staining) or the Ziehl–Neelsen staining method. Total vitamin D (25(OH)D3+D2) concentration was measured using the IDSSYSTEMS. The cutoff of this method is 7 ng/ml.

Patients were classified into 3 groups according to circulating total vitamin D concentrations: vitamin D deficient <20 ng/ml, vitamin D insufficient <30 ng/ml, and vitamin D sufficient ≥30 ng/ml [14]. The primary purpose of analysis was to assess the average vitamin D concentration in patients with MDR-TB and to compare the mean values to the general population. All interval data were presented in median values with interquartile range (IQR). Pearson's correlation test and ANOVA test were used to access the relationships between gender,
age, or comorbidity status and D vitamin concentration. The data were analyzed using the SPSS statistical system. A level of statistical significance was accepted at P ≤ 0.005.

3. Results

A total of 170 patients were included in the study. Their baseline characteristics are presented in Table 1. There were 128 males (75.3%), and 42 females (24.7%) with a median age of 47 years (IQR 34-54). Unilateral TB was found in 46.5% of patients, and 53.5% had bilateral TB. In 62.9% the lesion was destructive, while in 37.1% it was nondestructive. Sixteen patients (9.4%) died during hospitalization, 19 (11.2%) stopped treatment early, while 65 (38.2%) were cured. Seventy patients (41.2%) continue treatment. As for comorbidities, 21 patients (12.4%) were HIV positive and 19 (11.2%) had HCV infection. Twelve patients (7.1%) had HCV and HIV coinfection. Three patients (1.8%) had type 1 diabetes and 8 (4.7%) had type 2 diabetes.

Ten patients (5.9%) had hyponatremia (<135 mmol/l), 17 (10.0%) had hypernatremia (>145 mmol/l), six (6.5%) had hypokalemia (<3.5 mmol/l), and 36 (21.2%) hyperkalemia (>5 mmol/l) including 2 patients (1.2%) with severe hyperkalemia (≥6.0 mmol/l). Out of total, nine (5.3%) had hypocalcemia (<2.1 mmol/l), and 3 (1.8%) had hypercalcemia (>2.6 mmol/l). GFR <15 ml/min was found in only one patient as well as GFR 15-29 ml/min, GFR 30-59 ml/min was found in 6 (3.5%) patients, while GFR 60-89 was found in 18 patients. No patients had hypoglycemia (<3.9 mmol/l). 9.4% of patients had glucose concentration >5.9 mmol/l, 6.5% >7 mmol/l, 1.2% >10 mmol/l, and 0.6% >20 mmol/l. A CRP between 10 and 29 mg/l was found in 14.7% patients, 30-99 mg/l in 10.6% patients and >100 mg/l in 10.0% of patients.

Vitamin D concentration was determined in 75 cases (44.1%). 59 (78.7%) had vitamin D deficiency, 15 (20.0%) vitamin D insufficiency, and only 1 patient (1.3%) had optimal vitamin D concentration. The median concentration of vitamin D was 14.1 ng/ml (IQR 10.3-19.4). There was no statistically significant relationship between age (Pearson’s correlation test, r = −0.179, P = 0.124), gender (ANOVA test, F = 3.638 [critical value F = 4.00], P = 0.060), or comorbidities (ANOVA test, F = 0.677 [critical value F = 2.25], P = 0.691) and vitamin D status. TSH was determined in 84 patients and fT4 in 39 patients. The median TSH concentration was 1.76 mU/l

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Gender</th>
<th>Comorbidities</th>
<th>Localization in lungs</th>
<th>Laboratory parameters</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male n (%)</td>
<td>Female n (%)</td>
<td>HIV n (%)</td>
<td>HCV n (%)</td>
<td>HIV+HCV n (%)</td>
</tr>
<tr>
<td></td>
<td>128 (75.3)</td>
<td>42 (24.7)</td>
<td>21 (12.4)</td>
<td>19 (11.2)</td>
<td>12 (7.1)</td>
</tr>
</tbody>
</table>

HIV-Human immunodeficiency virus, HCV-Hepatitis C virus, CRP-C reactive protein, GFR-Glomerular filtration rate
(IQR 0.92-2.52) and fT4 concentration 1.02 ng/dl (IQR 0.90-1.09). Normal TSH was found in 78 patients (92.9%), while 6 patients (7.1%) had elevated TSH. All patients had normal fT4 concentrations.

4. Discussion

This retrospective observational study is the first to explore vitamin D status in MDR-TB patients in the Latvian population. In our studied population, there was a male predominance, which is similar to other studies where male gender was defined as a risk factor for MDR-TB [15]. In addition, there was no significant difference in vitamin D status between genders. In contrast, women in the healthy Latvian population tend to have higher vitamin D concentrations than men [13]. Furthermore, a statistically significant difference in vitamin D concentrations between different age groups was not found, contrary to the results of Mukane and Rasa [13], who reported higher vitamin D concentrations in the older Latvian population. Our data show that there is no significant difference in vitamin D concentration in HIV-MDR-TB coinfected patients in comparison to MDR-TB patients without HIV infection. Similarly, in a meta-analysis by Huang et al., vitamin D deficiency was not associated with an increased risk of TB in African HIV-infected patients [16], which supports our findings and lets us conclude that vitamin D deficiency is not a risk factor for MDR-TB development in HIV positive patients.

Our results indicate that the majority of MDR-TB patients, 78.7% in particular, had vitamin D deficiency, 20% insufficiency, and only one patient had optimal vitamin D concentration. This is in accordance with a similar study of the Latvian population conducted in the period from May 2007 to November 2011, where 54% had vitamin D deficiency, 29% insufficiency, while 17% had sufficient concentrations of vitamin D [13]. Similar data were presented in other studies, nevertheless it was concluded that results tend to vary among different ethnic and geographic groups, specifically in Asia [16,17]. The findings support the idea that MDR-TB patients tend to have lower vitamin D concentrations than those from the general population. Considering that sunlight is one of the main sources of vitamin D [9], in our previous study we compared seasonal (autumn, winter, spring, and summer) vitamin D concentrations in MDR-TB patients and the Latvian general population. Although MDR-TB patients had higher vitamin D concentrations during summer (median concentration 18.1 ng/ml), it was still significantly lower than in the general population (22.0 ng/ml). The most profound difference was seen during autumn (14.8 ng/ml vs. 22.9 ng/ml) [13]. A cohort follow-up study in Pakistan showed that low vitamin D concentrations are associated with the progression of active TB in healthy household contacts [10], and this might explain the higher susceptibility of women to disease progression. However, this contradicts our findings since we showed that males are more susceptible to MDR-TB than females who have higher vitamin D concentrations in general.

In a study by Rathored et al., it was suggested that low vitamin D concentrations may be linked to MDR-TB susceptibility in Indians [12], which is also in accordance with our study results. However, the unanswered question was whether vitamin D deficiency represents a risk factor or a consequence of TB itself. The analysis by Huang et al. [16] revealed that vitamin D deficiency was significantly associated with an increased risk of developing active TB in participants with latent TB and household contacts of TB patients. These results suggest that vitamin D deficiency is more likely a risk factor for TB rather than a consequence. The authors suggested that vitamin D is possibly involved in the early stage of TB infection development and symptom manifestation. This possibility was further strengthened by the finding that anti-TB treatment did not significantly affect vitamin D concentration in TB patients receiving treatment, and after completing anti-TB treatment, patients still had significantly lower vitamin D concentrations than controls without TB.

After demonstrating a strong association between vitamin D deficiency and TB, several potential pathway mechanisms have been described. A study by Eklund et al. [18] reported that vitamin D triggers an inflammatory response in human macrophages with enhanced secretion of interleukine-beta and that in patients with ongoing TB, human monocyte-derived macrophages can restrict MTB growth more effectively upon vitamin D stimulation. It was also shown that 1,25(OH)2D3 activates VDR signaling and induces antimicrobial responses such as induction of autophagy,
phagolysosomal fusion, release, and activation of the antimicrobial peptide cathelicidin, and killing of intracellular M. tuberculosis [16]. Interestingly, Selvaraj et al. [19] stated that 25(OH)D deficiency may be due to its increased use caused by CYP27B1 expression upregulation, which increases the conversion of 25(OH)D to 1,25(OH)2D3. Furthermore, Zeng et al. [20] found vitamin D concentrations ≤10 ng/mL to be significant risk factors associated with an increased risk for TB, vitamin D concentrations between 20 and 30 ng/mL to be potential risk factors, and vitamin D concentrations between 21 and 30 ng/mL to be not associated with an increased risk for TB progression.

With the promise of adding vitamin D supplementation to the cocktail of anti-TB drugs for effective TB treatment, several trials have searched for evidence. Unfortunately, so far, the results indicate that vitamin D supplementation does not significantly improve sputum smear conversion [12,21], does not improve clinical outcome, and has no overall effect on mortality. It was speculated that the ineffectiveness of vitamin D supplementation might be related to insufficient dosing [22]. As a result, a high-dose vitamin D regimen trial was conducted which found high doses of vitamin D to be safe and effective at correcting vitamin D deficiency, but unfortunately no improvement in sputum clearance was found [23], which was further confirmed by Xia et al. [24] in 2012. Nevertheless, we believe that the role of vitamin D supplementation in TB prevention needs further investigation.

Author contributions

LK gave the idea for the research, as well as the conception and design of the study. SU and RE contributed to the acquisition and interpretation of data. RE analyzed the data. SU drafted the article. LK and RE revised the article critically. SU, RE, and LK gave their final approval of the version submitted.

References


13. Mukane M, Rasa I. Vitamin D Status in Latvian Population: Data from Laboratory Databases, World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, Seville, Spain, 2-5 April; 2014.
