Case Report

A case series report of Tuberculosis patients with Vitamin D deficiency in Zambia

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ABSTRACT

An association of Vitamin D deficiency with Tuberculosis remains a valid assumption. It has been observed that TB is highly prevalent in certain ethnic groupings and regions of the world. Populations with darker skins are prone to vitamin D deficiency. The regions inhabited by people with darker skin coincides with high TB burden settings. Vitamin D has a key role in immune-modulation of the host response to *Mycobacterium Tuberculosis* infection. Studies have demonstrated early sputum culture conversion to negative, clinical recovery and radiological improvement with Vitamin D supplementation. However, there is currently no consensus on the advantages of this supplementation in TB treatment. We present the first case series report of pulmonary TB patients with severe deficiency of Vitamin D in Zambia. Additional data from randomised control studies is warranted.

INTRODUCTION

Tuberculosis (TB) is the second leading infectious cause of morbidity and mortality globally and the leading cause of death among people living with HIV.[1] Every 21 seconds a patient dies of a cause attributable to TB.[2] The emergence of drug-resistantTB has caused a paradigm shift in the global burden of TB, due to the complexity of regimens and the poor quality of life of affected patients.

The phenomenon of Vitamin D deficiency leading to reactivation of pulmonary tuberculosis (PTB) has been known since the nineteenth century.[3] Before the discovery of antibiotics, vitamin D was used to treat TB.[4] To date there are mixed views on the benefits of Vitamin D as an adjuvant therapy.[5]

There is evidence emerging that ethnicity influences susceptibility to TB infection and inflammatory response.[6,7,8] Populations with darker skins have a poor generation of vitamin D due to a high level of melanin which absorbs ultraviolet B radiation rendering it less available for Vitamin D production.[9] The high burden of TB coincides with regions inhabited by populations with darker skins.[10,11]

The association of Vitamin D deficiency and TB stems from the immune function of Vitamin D. It is known to be an immune modulator of the innate system. The phagolysosome function of macrophages and monocytes on mycobacterium is dependent on the availability of Vitamin D.[12] An elective visit to the TB treatment centre in Latvia where Vitamin D supplementation is routinely used as adjunct therapy in TB patients motivated us to evaluate three PTB patients.

PATIENT 1

A male,28years old, HIV negative of African ethnicity and diagnosed with primary TB. He presented to the University Teaching Hospital, a tertiary level institute in Zambia, with a two-month

history of ill-health characterised by fever, drenching night sweats, easy fatigue, loss of appetite and weight loss. He had no history of past TB or contact and was reported to have been healthy prior to this illness. He had no chronic medical conditions including renal disease. He reported spending most of his time outdoors prior to his illness and hospital admission**.** His diet comprised of maize meal, occasional fish (fresh or dry,) and mostly vegetable. He hardly had any fruits, juices and eggs.

On physical exam, he had temporal wasting, prominent clavicles, and ribs. His BMI was 19kg/m^2. His skin pigmentation was black. He was not in respiratory distress and had no finger clubbing. He was not pale or jaundiced. Respiratory examination revealed he had equal chest expansion and air entry. There were coarse crepitations bilaterally. Other systems were normal.

Laboratory results: PTB was diagnosed by GenexpertMTB/RIF which revealed a medium yield of MTB and no rifampicin resistance. Full blood count showed a raised white cell count (WBC). Liver and renal function tests were normal. Human immunodeficiency virus (HIV) serology was negative. He had insufficient Vitamin levels (See ***table 1***).

The patient responded well to the first line anti-tuberculous treatment, with fever subsiding and recovery of appetite in the second week of treatment. The patient was discharged after eight days of admission.

Table 1 Serum Vitamin D levels (done in August, 2 days post starting TB Treatment)

Parameter	Result	Unit	Biological reference
25 OH VITAMIN D Total	20.5	Ng/ml	Deficiency :<20 Insuffiency:20-29 Sufficiency: 30-100 Toxicity :>100

PATIENT 2

A42-year-old African male, HIV negative, with a history of alcohol misuse presented with a two-month history of a productive cough, poor appetite and weight loss. He had a past medical history of being treated for smear-positive TB on three occasions in2014, 2015 and 2016, respectively. He admitted to poor compliance in all three previous episodes.

He lived alone and survived on a small business, but due to his illness, it had become difficult to fend for himself. He could only afford a single unbalanced diet (maize meal with vegetables on most days). He admitted to abuse of alcohol but denied smoking.

On physical exam, he had dark black skin, was grossly wasted, had a BMI of 12.5kg/m^2, and his fingers were clubbed. Cardiovascular and respiratory examinations were normal. as were the gastrointestinal and central nervous systems.

Laboratory evaluation revealed a raised WBC. Liver and renal function tests were normal. Human immunodeficiency virus (HIV) serology was negative. Sputum microscopy revealed multiple acid-fastbacilli and X-pert MTB/RIF showed MTB detected but not rifampicin resistance. On Sputum microscopy and culture no organism could be found. The patient had insufficient serum Vitamin D levels (***See table 2***).

The recovery was very slow, he remained smear positive at one month of treatment however he showed clinical improvement in the second month of treatment and was eventually discharged after 7 weeks of admission.

Table 2: serum Vitamin D levels (done in August, 3 days post starting TB Treatment)

Parameter	Result	Unit	Biological reference
25 OH VITAMIN D Total	14.6	Ng/ml	Deficiency :<20 Insuffiency:20-29 Sufficiency: 30-100 Toxicity :>100

Patient 3

A Male aged 52 MDR-TB-HIV patient with a possibility of having bronchiectasis, on Atripla (TDF+3TC+EFV) and second-line anti-TB drugs. He had a previoushistory of absconding from treatment in the past year for both diseases. At the time of presentation, he was complaining of diarrhoea, anal sores, purulent right ear discharge and persistent cough. He was anorexic and could barely finish his food. On most days his diet comprised of maize meal with vegetables and dry Kapenta (freshwater sardines). He had a history of alcohol abuse.

Despite being on second line anti-TB drugs with good directly observed therapy for four months, he remained smear positive with sputum grade of 2+. Due to lack of sputum conversion at month 4 and a worsening clinical condition, second line DST by line probe assay showed no new resistance.

On Physical examination, he was fully conscious but emaciated with BMI of 16.5 kg/$m^{2.}$ He was not in respiratory distress, had finger clubbing, with obvious suppurative otitis media. Respiratory examination revealed crepitations bilaterally. The cardiovascular, gastrointestinal and nervous systems were unremarkable.

Laboratory tests showed HIV viral load of 57 copies/ml. He had, normal renal function. Full blood count revealed a normal white cell count and normocytic normochromic anaemia. Serum Vitamin D was deficient (***See table 3***).

The patient clinical status worsened with no improvement in sputum grade and he died after two months of standardisedsecond-lineanti-tuberculousdrugs (Kanamycin + Levofloxacin + cycloserine e + Ethionamide + Pyrazinamide).

Table 3: Serum Vitamin D (done in August and 17 days post second line ATT

Parameter	Result	Unit	Biological reference
25 OH VITAMIN D Total	13.4	Ng/ml	Deficiency :<20 Insuffiency:20-29 Sufficiency: 30-100 Toxicity :>100

DISCUSSION

This is the first case series report of vitamin D deficiency in PTB patients in Zambia. Vitamin D influences the macrophages in their phagocytosis action and deficiency renders one susceptible to TB.[3,12]

Intervention studies done have shown the benefit of vitamin D supplementation.[13,14] A Metanalysis by Wallis and Zumla found vitamin D supplementation to be well tolerated and safe but with concern on the paradoxical reactions.[15] In Zambia Vitamin D supplementation has not been adopted as standard practice hence supplementation could not be done for the patients mentioned above.

Vitamin D as adjuvant therapy shortens the MTB clearance in sputum and aids speedy improvement of radiological features.[16,17]

Paradoxical reactions have been observed in a few cases of vitamin Das an adjunct therapy. The mechanism for this reaction is unestablished.[18]

Vitamin D level varies with respect to the season. The levelstend to drop during winter as there is usually cloud cover which blocks ultraviolet B radiation. In addition, people tend to spend most times indoors during the cold seasons.[19]

In the Zambia, the effect of cloud cover may not be relevant as during the cool-dry season the sky is clear and there is adequate exposure to ultraviolet B radiation.[20]

None of the three patients described above had foods that provide vitamin D in their diet. This could be another contributing factor.[21]

One vital observation made in the three patients is that the patient with the lowest Vitamin D (patient 3) failed to recover and the other with deficiency (patient 2) but slightly higher than patient 3 had a prolonged recovery period. The observation made in the three patients is in line with existing evidence that Vitamin D impacts positively on recovery from *Mycobacteria Tuberculosis*.[17]

Patient 3 despite being virally suppressed, hadimpaired CD4 recovery this is in line with. Mariam et alwhofound that Vitamin D insufficiency is associated with late CD 4 recovery in patients with advanced HIV on HAART.[22,23] It's possible that severe Vitamin D deficiency led to the progression of both the HIV disease and TB infection. This requires further understanding.

CONCLUSION

The evidence so far links vitamin D deficiency with increased susceptibility to TB infection and reactivation Severe Vitamin D deficiency could be associated with poor outcome. Longitudinal studies are needed to demonstrate association, efficacy and safety of its supplementation.

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