

HOW FREQUENTLY ARE PEOPLE WITH NEWLY DIAGNOSED PULMONARY TUBERCULOSIS DEFICIENT IN VITAMIN D LEVELS IN KHYBER PAKHTUNKHWA: A PILOT STUDY PROJECT

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ABSTRACT

Objective: To estimate the frequency of vitamin D deficiency in patients with newly diagnosed pulmonary tuberculosis in Khyber Pukntunkhwa.

Methodology: It was a descriptive cross sectional study conducted in a private consulting clinic at Ibrahim Hospital, Dabgari Gardens, Peshawar from 01 April, 2014 to 30 June 2015. A total of 194 patients of either gender, between 15 to 70 years of age with newly diagnosed pulmonary tuberculosis were included in the study. 10cc of blood was obtained under strict aseptic technique and immediately sent to laboratory to estimate vitamin D levels.

Results: Of the 194 patients included, 108(55.67%) were male and 86(44.33%) were females. Male to female ratio was 1.26:1. The frequency of vitamin D deficiency in patients suffering from pulmonary tuberculosis was observed in 82(42.27%) while 112(57.73%) were having normal vitamin D levels. More females 49(57%) were suffering from Vitamin D Deficiency compared to males 33(30.6%).

Conclusion: Patients with pulmonary tuberculosis are significantly Vitamin D deficient. This deficiency was more marked in females.

Key Words: Pulmonary TB, Vitamin D deficiency

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INTRODUCTION

Tuberculosis (TB) is known to infect 1 out of 3 individuals across the globe¹. Only in 2010 alone, a staggering 8.8 million new cases of TB were reported. According to a report of WHO resulting in alarming 1.1 million and 0.35 million people dying of TB in HIV- negative population and positive population respectively¹. 10 million children in 2009 lost their parents secondary to TB². The figures are no different in the US with case detection rates in 2011 of 16 % in whites and 84 % in minority's population³. In Pakistan, the estimated incidence of TB (all types included) was 231 per 100000 population In 2011⁴. These figures led to a staggering case detection rate of 64 % in Pakistan in year 2011⁴. It remains a possibility that the case detection rate may not be the same across the country with difference in various regions. Ironically despite a high prevalence of TB, we still don't have reliable figures for the exact prevalence⁵.

Vitamin D deficiency is considered to be major pub-

lic health problem. The people living in tropics are not immune to deficiency where they have ample sun exposure and have cutaneous synthesis. Multiple epidemiological studies over a period of time in the South Asian population have shown low serum levels of Vitamin D in general population^{6,7}.

It is now a well-established fact relating to the chances of developing TB secondary to deficient stores of vitamin D⁸. In vitro observations have suggested that the growth of *M. tuberculosis* inside the macrophages can be suppressed by exogenous vitamin D supplements⁹. Although the exact mechanism remains poorly understood but it is thought that the up regulation by vitamin D of NO, NADPH oxidase, cathelicidin, and autophagy mechanisms in macrophages¹⁰.

It is not uncommon to find low levels of Vitamin D across the world, especially prevalent in developing countries⁹. The major factors thought to be responsible are the food fortification policies, geographic locations, varied demographic features and season. ⁸ The popu-

lation is more likely to develop TB if they are vitamin D deficient⁷. Kibirige et al reported in TB hospitalized patients alarming figures of vitamin D deficiency (44.2%), insufficiency (23.5%), severe (13.5%) and very severe vitamin D deficiency (4.2%).¹¹ In another study by Chaudhary et al, 26.66% of individuals with TB had vitamin D deficiency as compared to controls (7.69%)¹². Vitamin D deficiency was reported in 57% of TB cases (mean 23.23 ±6.81ng/ml) as compared to 33% in controls (mean 29.27±8.89 ng/ml) ($p < 0.0001$) in a large scale study in Karachi⁷.

The present pilot study was designed to estimate the frequency of vitamin D deficiency in individuals with newly diagnosed pulmonary TB. The need for doing this study project was solely felt because of lack of any data in Khyber Pakhtunkhwa. The study results are expected to provide us with local data about the magnitude of the problem and the results can be used as first hand local evidence for future research and recommendations can be developed for prevention and control.

METHODOLOGY

It was a cross sectional descriptive study using non-probability consecutive sampling technique conducted in a private consulting clinic at Ibrahim Hospital, Dabgari Gardens, Peshawar. The study duration was 15 months from 01 April, 2014 to 30 June 2015. Informed written consent was taken from all patients after elaborating the purpose and benefits of the project. A total of 194 patients of either gender, belonging to Khyber Pakhtunkhwa, between 15 to 70 years of age with newly diagnosed pulmonary tuberculosis were enrolled in the study. Individuals with already diagnosed osteomalacia or vitamin D deficiency evident from past medical records, with renal or hepatic impairment, with chronic illness like diabetes and cancer, on oral or parenteral vitamin D supplementation, with extra pulmonary TB or with previously diagnosed or treated for pulmonary tuberculosis were excluded from the study.

From all the patients at inclusion, 10cc of blood was obtained under strict aseptic technique and immediately sent to laboratory to estimate vitamin D levels. All the samples were analyzed in one single laboratory. Special proforma was designed to record the data.

Data were analyzed using SPSS version 20. Mean± standard deviation were calculated for quantitative variables like age, serum vitamin D level while frequency / percentages were calculated for categorical variables like gender and vitamin D. To see the effect modification, vitamin D deficiency was stratified among the age and gender. Chi-square test using p value ≤ 0.05 as significant was used for post stratification.

RESULTS

Of the 194 patients included, 108(55.67%) were male and 86(44.33%) were females making a ratio of 1.26:1. The age distribution of the sample is shown in table 1. The vitamin D deficiency in individuals suffering from pulmonary TB was observed in 82(42.27%) while 112(57.73%) were having normal vitamin D levels. Age wise distribution of vitamin D deficiency among pulmonary TB is shown in table 2 while gender distribution is shown in table 3.

DISCUSSION

TB over decades has been a global health issue. Better knowing of the various pathogenic mechanisms responsible for the disease occurrence and progression would enable us to devise future treatment and preventive strategies. Host immunity against TB consists of both innate and adaptive immune responses^{13,14}.

Of the total world population, about one third (2 billion) are known to be suffering from TB¹⁵. It is the developing countries including India, Pakistan, Bangladesh, China and Africa that report the bulk of new cases with reported rates as high as 100/100,000 or higher¹⁵. Among the top 22 countries with high TB risks, Pakistan ranks sixth, and hence is thought to be contributing 43% of the disease burden towards the Eastern Mediterranean region, according to the WHO¹⁶.

It is a well-known fact that the vitamin D causes activation of the macrophages and stales the growth of MTB with resultant protection against TB^{17, 18}. Across the globe low levels of vitamin D have been reported especially in the developing countries. The difference in the prevalence across various regions of the world is thought to be secondary to the differences in the food fortification policies, demographic and geographic distribution and seasons^{7,8,19}. Several biological studies have confirmed the beneficial role of vitamin D on the immune system resulting in the suppression of proliferation of Mycobacterium TB and resulting secondary generalized inflammatory response^{20, 21}.

It was more than 20 years ago that a possible association between low levels of vitamin D and predisposing to TB were first reported²². Multiple studies in individuals with active TB in Gujarati community in India²³, African living in London²⁴, African immigrants residing in Australia²⁵ and people of West Africa²⁶ have reported low vitamin D levels as compared to general population not suffering from TB. In all of the above studies, approximately half of the healthy females with no illness including TB were found to have low levels of vitamin D. The results suggested that a major proportion of healthy adults are deprived of the beneficial effects of vitamin D. We are not sure of the exact mechanism responsible for vitamin D deficiency being more common in the female population but it's probably because the

Table 1: Age wise distribution of patients (n=194)

| Age Groups | Frequency | Percent |
|------------|-------------------|---------|
| < 30 | 24 | 12.4 |
| 31- 45 | 84 | 43.3 |
| 46- 60 | 79 | 40.7 |
| > 60 | 7 | 3.6 |
| Total | 194 | 100 |
| Mean±SD | 44.52±11.48 years | |

Table 2: Age wise distribution of vitamin D deficiency (n= 194)

| | | Vitamin D Deficiency | | Total | P-value |
|----------------|---------|----------------------|--------|-------|---------|
| | | Yes | No | | |
| Age (in years) | < 30 | 7 | 17 | 24 | 0.570 |
| | | 29.2% | 70.8% | 100% | |
| | 31 - 45 | 38 | 46 | 84 | |
| | | 45.2% | 54.8% | 100% | |
| | 46 - 60 | 34 | 45 | 79 | |
| | | 43.0% | 57% | 100% | |
| | > 60 | 3 | 4 | 7 | |
| | | 42.27% | 57.73% | 100% | |
| Total | 82 | 112 | 194 | | |

Table 3: Gender wise distribution of vitamin D deficiency (n=194)

| | | Vitamin D Deficiency | | Total | P-value |
|--------|--------|----------------------|--------|-------|---------|
| | | Yes | No | | |
| Gender | Male | 33 | 75 | 108 | 0.000 |
| | | 30.6% | 69.4% | 100% | |
| | Female | 49 | 37 | 86 | |
| | | 57.0% | 43.0% | 100% | |
| Total | 82 | 112 | 194 | | |
| | | 42.27% | 57.73% | 100% | |

females are more housebound with inadequate exposure to sun, comparatively poor nutritional status, less access to health care as compared to males, social stigma in partner with TB, which makes them reluctant from seeking early medical care, and in some places, culture of wearing hooded cloaks (Burqas). Nevertheless the prevalence of Vitamin D insufficiency was reported much lower than what was found in another study conducted in Karachi²⁷. Interestingly, in 2010, Mansoor et al in Karachi carried a bone health survey and found 82.8% women with Vitamin D deficiency²⁸. The disparity in the reported results in this study compared to the previous can well be explained by the smaller sample size, dark skin complexion in Karachi with additional betel chewing habit and different cut off limit of Vitamin D deficiency levels.

We observed the frequency of deficient vitamin D levels in 42.27% of patients suffering from newly diagnosed tuberculosis. Our results of vitamin D deficiency were in concordance with the Japanese study involving TB patients not infected with HIV(13.2 ± 8.82 ng/mL vs. 13.7±5.9 ng/mL, 83.0% vs. 87.0%)²⁹. Across the world in different continents, various studies have shown that vitamin D levels are low in individuals with TB as compared to the healthy subjects. Different studies in parts of India³⁰, Europe³¹, Africa³², and Asia³³ have confirmed the positive association. Cahill in 2011 published a case report and postulated very low levels of Vitamin D in patients with both primary and reactivation cases of TB³⁴.

Interestingly there are studies done which show higher³⁵ or no difference³⁶ in the vitamin D levels in

healthy controls and patients with TB. On critical analysis of these studies, we believe that there was not enough information about the included subjects and no account was taken to control the confounders like associated diabetes and malignancy³². There is possibly a bilateral mechanism between the occurrence of TB and vitamin D metabolism. The primary mechanism responsible in predisposing to TB is reduction in cell mediated immunity responsible for causing TB and later deficiency in vitamin D levels. Nevertheless infection with TB itself can also be responsible for the fall in Vitamin D levels³⁶. It is a well-established fact that low vitamin D levels severely hamper the cathelicidin production by the macrophages with resultant increased chances of TB³⁷. Vitamin D receptor polymorphisms are thought to be another mechanism associated with increased chances of TB.³³ Individuals who are replete with vitamin D are observed to have low chances suffering from TB and high tuberculin-negative reactions³⁵. The treatment responses are observed to be poor in TB deficient individuals³⁸.

CONCLUSION

Patients with tuberculosis are significantly Vitamin D deficient. This deficiency is more marked in females and may well be one of the major factors responsible for the higher susceptibility and disease progression.

RECOMMENDATIONS

Large multicenter trials involving the infected and the general population should be initiated to establish the exact prevalence of vitamin D deficiency in our local population. Large scale studies are needed to prove or refute if routine Vitamin D supplements can be protective against TB or have favorable outcomes during treatment of individuals in countries like Pakistan.

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CONTRIBUTORS

MTM conceived the idea, planned the study, and drafted the manuscript. HK helped acquisition of data and did statistical analysis. NUI supervised the study and critically revised the manuscript. All authors contributed significantly to the submitted manuscript.