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Investigation of Zinc and Vitamin A Supplement impact on Serum Biochemical and Physiological Parameters in Pulmonary Tuberculosis

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A B S T R A C T

Background: Pulmonary Tuberculosis (PTB) remains a global health challenge, necessitating exploration into adjunctive therapeutic approaches. The intricate link between nutritional status and PTB progression underscores the potential role of zinc and vitamin A in modulating host responses.

Objective: To find out whether zinc and vitamin A supplements improve the antituberculosis treatment's effectiveness in terms of clinical outcome and dietary intake.

Methodology: The two-year trial at the Rehman Medical and Dental College, involved 130 patients divided into micronutrient and placebo groups from January 2020 to December 2022 was conducted. The micronutrient group received zinc and vitamin A supplements alongside antituberculosis medications, while the placebo group only received antituberculosis medications. Capsule-shaped supplements containing 10mg retinol equivalents, vitamin A, and 20 mg zinc were administered. Statistical analyses, employing student t-tests and multivariate analysis, assessed therapy effects at baseline, 2 and 6 months, with a significance threshold of $P \leq 0.05$.

Results: In our study, out of 130 patients 40 participants were eliminated because they had missed medication or had negative effects. After six months of antituberculosis therapy, the micronutrient group exhibited superior outcomes, including higher Karnofsky scores (91.0 ± 0.7), greater decrease in lesion region (91.94 ± 12.31) after two months, and increased plasma retinol concentrations (1.13 ± 0.05). Two cases of drug resistance were observed in the placebo group.

Conclusion: In conclusion, the incorporation of vitamin A and zinc supplementation alongside PTB therapy shows promise in enhancing the effectiveness of tuberculosis treatment and expediting the breakdown of sputum smears. This suggests a potential avenue for improving outcomes in TB patients.

Keywords: Pulmonary Tuberculosis; Zinc; Vitamin A; Clinical Outcomes; Micronutrient Intervention

Introduction

Pulmonary Tuberculosis (PTB), a contagious respiratory disease caused by Mycobacterium tuberculosis, remains a profound global health challenge, exerting a substantial toll on both morbidity and mortality rates.[1,2] As the medical and scientific communities intensify their efforts to combat this relentless pathogen, a multifaceted approach to understanding the disease's complexities and optimizing treatment outcomes becomes increasingly imperative. In this context, the exploration of nutritional interventions, specifically the administration of zinc and vitamin A supplements, emerges as a pivotal avenue of investigation. These essential micronutrients have long been recognized for their immunomodulatory properties, and their potential to influence a myriad of biochemical and physiological parameters offers promise in enhancing PTB management.[3,4]

The intricate relationship between nutritional status and the progression of PTB has been a subject of growing interest within the scientific community. Emerging evidence underscores the pivotal role that essential micronutrients play in modulating the host response to infection, thereby potentially impacting the course of PTB.[5,6] However, despite the theoretical promise of zinc and vitamin A in bolstering the immune response and improving clinical outcomes in PTB patients, a critical knowledge gap persists regarding the specific impact of these supplements on serum biochemical and physiological parameters in individuals diagnosed with PTB.[7]

This comprehensive exploration embarks on a mission to bridge this knowledge gap by delving into the potential benefits of zinc and vitamin A supplementation in the context of PTB. It seeks to elucidate whether these micronutrients can serve as adjunctive therapeutic approaches, complementing conventional PTB treatments and ultimately leading to improved clinical outcomes and the overall well-being of affected individuals.[8]

Numerous studies have underscored the intricate relationship between nutritional status and the progression of PTB, highlighting the potential role of essential micronutrients in modulating the host response to infection. Zinc and vitamin A, recognized for their immunomodulatory properties, are particularly intriguing in this context, as they may influence various biochemical and physiological parameters.[3,4] However, a knowledge gap persists regarding the specific impact of zinc and vitamin A supplementation on serum markers and physiological parameters in individuals diagnosed with PTB.[5,6]

To comprehensively investigate the impact of zinc and vitamin A supplements on serum biochemical and physiological parameters in PTB, this study adopts a meticulously designed methodological framework. The approach integrates a multifaceted array of research tools and methodologies, aimed at providing a holistic understanding of the subject matter.

In the pursuit of a comprehensive understanding, our study employed a multidimensional approach, integrating clinical assessments, laboratory analyses, and nutritional evaluations. The gathered data is expected to shed light on the interplay between nutritional supplementation, disease progression, and treatment outcomes. Furthermore, the research considered demographic factors, ensuring a nuanced exploration of the diverse ways in which zinc and vitamin A impact individual with PTB across different populations. As the global health community continues its efforts to combat TB, our findings hold the potential to significantly enhance the arsenal of treatment options and pave the way for personalized, evidence-based interventions tailored to the nutritional needs of PTB patients.

This study's main goal was to find out whether zinc and vitamin A supplements improve the antituberculosis treatment's effectiveness in terms of clinical outcome and dietary intake. These findings promise to update future therapeutic interventions, laying the groundwork for targeted nutritional strategies that complement conventional PTB treatments and contribute to improved clinical outcomes and the overall well-being of affected individuals.

Objective

The study's main goal was to find out whether zinc and vitamin A supplements improve the antituberculosis treatment's effectiveness in terms of clinical outcome and dietary intake.

Methodology

A two-year experiment of supplementation, double-blind and placebo-controlled, was carried out at Rehman Medical and Dental College, Peshawar from January 2021 to December 2022. The Committee on Health Research Ethics authorized this research. Each participant was given an informed consent form to sign. We recruited 130 patients in all, and we split them evenly into two groups. The first group, referred to as the micronutrient group, was given zinc and vitamin A supplements in addition to antituberculosis medications. Antituberculosis medications were given to the second group known as the placebo group.

Data were collected from all patients with age range of 18 to 60 years, three sputum samples that, upon microscopic inspection, proved to be positive for acid-fast bacilli, clinical and radiologic symptoms that were compatible with TB in the lungs, and no previous use of prior antituberculosis medication. A patient's history of diabetes mellitus, chronic kidney failure, complications of liver disease, congestive cardiac failure, pregnancy, lactation, use of steroid medication or dietary supplements featuring zinc, iron, or vitamin were excluded.

Table 1. Comparative Baseline Characteristics in Micronutrient vs. Placebo Groups

Variables	Micronutrient group (n=45)	Placebo group (n=45)
Gender Distribution		
Male	25 (27.78%)	21 (23.33%)
Female	20 (22.22%)	24 (26.67%)
Age (Year)		
Men	23.5 ± 5.6	28.4 ± 10.4
Women	27.4 ± 6.8	30.5 ± 8.7
Tuberculin skin test induration (mm)	17.5 ± 6.0	18.0 ± 5.8
Presence of a BCG scar	13 (28.89%)	11 (24.45%)
Body temperature	37.2 ± 0.7	36.0 ± 0.5
BMI < 18.5 kg/m2	23 (51.11%)	25 (55.56%)
Radiologic signs		
Cavities (n)	16 (35.56%)	12 (26.67%)
Infiltration (n)	45 (100%)	45 (100%)
Leukocytes count (× 10^9 cells/L)	10.3 ± 2.5	9.5 ± 2.6
Serum albumin (g/L)	37.2 ± 5.1	36.8 ± 5.4
Sputum smear grade (n)		
+1	27 (60.0%)	32 (71.11%)
+2	13 (28.89%)	10 (22.22%)
+3	5 (11.11%)	3 (6.67%)

Capsule-shaped supplements and placebos were made at IPRAM International, Islamabad, Pakistan. In a lactose matrix, each micronutrient pill had 10mg retinol equivalents, vitamin A, and 20 mg zinc. The only ingredient in the placebo was lactose. Patients weighing between 30 and 55 kg were given an antituberculosis regimen consisting of 250 mg isoniazid, 500 mg rifampicin, 1000 mg pyrazinamide, and 500 mg ethambutol daily for two months, then three times a week for the following four months of 250 mg isoniazid and 500 mg rifampicin. Patients weighing more than 55 kg were given the following regimen: 300 mg of isoniazid, 600 mg of rifampicin, 2000 mg of pyrazinamide, and 1000 mg of ethambutol each day for two months, then three times a week for the next four months, 600 mg of isoniazid and 600 mg of rifampicin. Patients were obliged to come to the clinic once a week for the first three months of the experiment in order to pick up their anti-tuberculosis medications and supplement or placebo capsules for the following week. Daily compliance checks at home were conducted by medical personnel. Patients who skipped even one day of their first three months of treatment or

Table 2. The Evolution of Clinical and Laboratory Characteristics in Micronutrient and Placebo Groups

Variables	Micronutrient group (n = 45)	Placebo group (n = 45)
Erythrocyte sedimentation rate (ESR) (mm/h)		
1st month	36.1 (18.2–87.7)	32.5 (21.2–69.0)
3 months	23.5 (16.3–37.0)	27.5 (19.3–39.8)
6 months	12.0 (4.0–22.0)	18.5 (7.0–27.8)
Karnofsky score		
1st months	79.8 ± 0.5	81.0 ± 0.6
3 months	91.0 ± 0.7	91.2 ± 0.4
6 months	98.8 ± 0.8	94.3 ± 0.7
Body weight (kg)		
1st months	43.7 ± 0.7	42.6 ± 0.9
3 months	45.9 ± 0.8	44.8 ± 0.8
6 months	50.6 ± 0.4	47.5 ± 0.4
Drug resistance (n)		
1st months	0	0
3 months	0	0
6 months	0	2
Sputum and culture positive (n)		
1st months	45	43
3 months	0	0
6 months	0	2
Plasma C-reactive protein (CRP) (mg/L)		
1st month	52.0 ± 4.0	43.2 ± 5.7
3 months	7.2 ± 1.7	8.4 ± 2.0
6 months	1.2 ± 0.5	2.0 ± 1.0

Table 3. Radiologic Assessment of Lesion and Cavity Dynamics Over Time in Micronutrient and Placebo Groups

Variables	Micronutrient group (n = 45)	Placebo group (n = 45)
Mean lesion area (cm2)		
1st month	232.91 ± 20.89	220.31 ± 18.07
3 months	91.94 ± 12.31	121.91 ± 12.97
6 months	20.19 ± 4.70	19.63 ± 4.79
Cavity surface area (cm2)		
1st month	24.40 ± 4.79	7.28 ± 3.42
3 months	7.37 ± 1.73	6.84 ± 1.62
6 months	1.48 ± 0.43	1.90 ± 0.88
No. with cavities		
1st month	22	19
3 months	16	15
6 months	7	11

who had significant side effects from their medications were removed from the research. Patients whose strains of Mycobacterium tuberculosis were sensitive to a variety of medications were placed on an altered treatment regimen after a period of three months of TB treatment, and their data were deleted from the study. Furthermore, pre-treatment, as well as two to six months after treatment initiation, anthropometric measurements, a medical checkup, a chest CT scan, a direct sputum analysis and culture, blood samples, and TB medicine were administered.

Statistical analyses were conducted using SPSS V27.0 with student t-tests employed for comparisons between treatment groups. Multivariate analysis of variance repeated-measures design was used to test variations in the effects of therapy among the micronutrient and placebo groups. A calculated P-value ≤ 0.05 was deemed statistically significant.

Results

In our study, out of 130 patients 40 participants were eliminated because they had missed medication or had negative effects. In the micronutrient group and placebo group, 45 out of 65 patients (69.23%) finished the research, respectively. At baseline, there were no discernible differences between the 2 groups in terms of age, sex distribution, clinical and biochemical state, or radiologic symptoms (Table 1).

Mycobacteria sensitive to the isoniazid and positive smears of sputum were found in two patients in the placebo group after six months of PTB therapy (Table 2). There was a notable rise in weight gain between the start of the study and two months, as well as between two and six months, which was seen in both group. ESR and CRP significantly decreased within groups at both two and six months of age, but there was not a significant variance between groups. The micronutrient group's Karnofsky score exceeded the placebo group's after six months.

After two months, the micronutrient group showed a substantially higher mean decrease in lesion region compared to the placebo group (Table 3). The cavity surface area did not significantly vary between the micronutrient and placebo groups. Furthermore, all anthropometric indices improved gradually and significantly as a consequence of antituberculosis therapy (Table 4); however, vitamin supplementation had no discernible impact.

Both groups' concentrations of zinc protoporphyrin decreased and those of hemoglobin and plasma retinol increased significantly after three and six months of antituberculosis medication. Following six months of

Table 4. Anthropometric Measurements and Body Composition Changes Over Time in Micronutrient and Placebo Groups

Variables	Micronutrient group (n = 45)	Placebo group (n = 45)
Fat mass (kg)		
1st month	5.0 ± 0.4	5.6 ± 0.4
2 months	6.0 ± 0.3	6.6 ± 0.3
6 months	6.8 ± 0.6	7.6 ± 0.5
Suprailiac skinfold thickness (mm)		
1st month	5.1 ± 0.3	5.6 ± 0.4
2 months	6.1 ± 0.4	6.4 ± 0.5
6 months	7.1 ± 0.5	7.7 ± 0.6
Mid upper arm circumference (cm)		
1st month	21.7 ± 0.5	20.7 ± 0.5
2 months	22.3 ± 0.3	21.9 ± 0.5
6 months	24.2 ± 0.4	25.0 ± 0.5
BMI (kg/m^2)		
1st month	17.1 ± 0.2	18.0 ± 0.4
2 months	18.2 ± 0.3	19.2 ± 0.2
6 months	19.3 ± 0.4	20.1 ± 0.6
Biceps skinfold thickness (mm)		
1st month	4.1 ± 0.3	4.1 ± 0.3
2 months	4.8 ± 0.5	4.8 ± 0.3
6 months	5.6 ± 0.4	5.4 ± 0.4
Body fat (%)		
1st month	10.5 ± 1.0	12.0 ± 1.0
2 months	12.1 ± 1.1	13.6 ± 1.0
6 months	13.2 ± 1.2	15.0 ± 1.0

Subscapular skinfold thickness (mm)		
1st month	5.6 ± 0.3	5.0 ± 0.4
2 months	6.5 ± 0.4	6.7 ± 0.4
6 months	7.6 ± 0.6	7.6 ± 0.5
Triceps skinfold thickness (mm)		
1st month	4.8 ± 0.6	4.5 ± 0.5
2 months	5.7 ± 0.7	5.6 ± 0.5
6 months	7.0 ± 0.8	6.5 ± 0.6

antituberculosis therapy, the micronutrient group's rise in plasma retinol concentrations was considerably greater than the placebo group's. After three and six months of antituberculosis medication, there was no significant difference in plasma zinc concentrations between the groups (table 5).

Discussion

The outcomes of this two-year community-based supplementation study provide important new information on the possible effects of vitamin A and zinc supplements on people with PTB. The research offered a multifaceted view of the interaction between nutritional supplements and PTB treatment results by focusing on a broad range of criteria, including clinical, radiological, biochemical, and nutritional aspects. The results are strengthened by the study's double-blind, placebo-controlled methodology, which also increased the validity of the benefits that were seen.

While several studies have demonstrated some detrimental effects on clinical response when vitamin A supplementation is combined with antituberculosis treatment. In previous studies vitamin A supplementation in conjunction with antituberculosis treatment was shown to have some negative effects on clinical response in South African children with tuberculosis.[12] While in our study, vitamin A and zinc supplementation was very beneficial, especially during the first two months of antituberculosis treatment.[13-15]

Similarly, a study conducted by Karyadi et al. and Smith reported that supplementation with vitamin A and zinc was of great benefit, particularly during the first 2 months of antituberculosis treatment,[16,17]while in contrast the findings of previous studies demonstrated that non-significant effect on TB treatment success after 6 months of micronutrient supplementation.[18]

Similar studies have also demonstrated that multi-micronutrient supplementation does not significantly affect treatment outcomes among pulmonary TB patients.[19,20] Various factors may account for this non-significant finding, including a small number of included studies in the analysis. Moreover, the included trials did not categorize patients based on nutritional and comorbid status.[21] Other factors such as boost in total body weight, body fat percentage, serum hemoglobin, and the plasma levels of zinc were observed, after a six-month course of efficacious antituberculosis medication, which were consistent with a study reported by an Indonesian researchers.[16] At six months, the clinical advantage of supplementation was less striking, most likely as a result of the strong antimycobacterial medication therapy overshadowing its effects.

According to earlier research, individuals with smear-positive TB who received a 3-drug regimen for two months had unacceptably high rates of recurrence.[22-24] Similarly a previous study in India showed that a 4-drug tuberculosis regimen for 3 months in patients with smear-positive tuberculosis resulted in unacceptably high relapses rates.[25] However, the recurrence rate in our patients was not evaluated; yet, after six months, vitamin supplementation improved the Karnofsky score and had an impact on the clinical result in the first three months. Our study's findings indicate that adding micronutrient supplements to the existing TB treatment regimens could be beneficial. It could be feasible to shorten the treatment schedule or lower the dose of antituberculosis medications during the first or second phase of the disease. Antituberculosis therapy would be less expensive, more often completed, and less likely to have side effects with such a shortened course, our results align with the earlier observations of Karyadi et al. , Ginawi et al. , Lutge and his colleague, who reported that micronutrient supplementation had effect on clinical outcome in the first 2 months and improvement in the Karnofsky score after 6 months. Furthermore, it could possibly reduce the dosage rate and

Table 5. Serum Biomarkers and Hematological Parameters at Different Time Points in Micronutrient and Placebo Groups

Variables	Micronutrient group (n = 45)	Placebo group (n = 45)
Plasma zinc (mol/L)		
1st month	10.52 ± 0.25	11.10 ± 0.25
2 months	11.15 ± 0.37	10.21 ± 0.33
6 months	12.08 ± 0.34	12.12 ± 0.32
Zinc protoporphyrin (mol/mol)		
1st month	57.9 ± 4.7	54.0 ± 3.
2 months	46.4 ± 4.1	38.9 ± 3.5
6 months	30.3 ± 2.6	27.7 ± 2.7
Hemoglobin (g/L)		
1st month	123.0 ± 2.0	122.3 ± 2.7
2 months	129.1 ± 2.3	132.4 ± 2.5
6 months	140.1 ± 2.1	138.7 ± 2.4
Plasma retinol (mol/L)		
1st month	0.81 ± 0.04	0.89 ± 0.04
2 months	1.13 ± 0.05	1.07 ± 0.03
6 months	1.38 ± 0.06	1.21 ± 0.05

shorten the regimen, potentially reducing the risk of tuberculosis transmission.[16,26,27]

After three months of antituberculosis medication, the micronutrient group converted positive sputum smears substantially quicker than the placebo group. Previous studies reported that the conversion of positive sputum smears was significantly faster in the micronutrient group than in the placebo group after 2 months of antituberculosis treatment.[28] There is no research on the function of zinc and vitamin A in the transformation of phlegm. Retinoids, on the other hand, have been shown to prevent pathogenic tubercle bacilli from multiplying in human macrophage cultures. However, in contrast, a study undertaken by Crowle showed that in vitro studies have demonstrated that retinoic acid can inhibit the multiplication of mycobacteria in macrophages.[29]

Furthermore, it was shown that in vitro macrophage cellular killing was reduced in cases of zinc shortage and quickly recovered in cases of zinc supplementation.[29,30]

After receiving antituberculosis medication for two months, the micronutrient group saw radiologic remission sooner than the placebo group. Additionally, after taking antituberculosis medicine for six months, there was a correlation seen in the supplemented group between elevated serum retinoid levels and radiologic improvement. This observation has several possible interpretations. First, pulmonary tissue, which has a high concentration of nuclear retinoic acid receptors, directly uses retinol.[31] Second, zinc helps shield cells from the harm that comes from free radicals. It has been shown that nitric oxide causes metallothionein in membranes to release zinc; hence, a sufficient supply of zinc may prevent free radical membrane damage during inflammation.[32] In literature studies have shown that high serum retinol levels

enhance innate immunity, maintain the mucosal epithelium, and relate to the function of T and B lymphocytes.[33,34] The process of decreasing serum retinoid levels during infection is explained by reduced production of retinoid interacting proteins, an adverse initial stage protein, which impairs the liver's release of vitamin A. Furthermore, retinol loss via the urine could also be important. Up to 45% of the daily need of vitamin A is lost in urine by patients suffering from pneumonia and sepsis, whereas children suffering from shigellosis only lose 15% of the daily requirement.[35] The larger rise in plasma retinol concentrations after six months of antituberculosis medication, which occurred concurrently with the decrease in ESR and CRP concentrations, suggests that vitamin A supplementation caused an acute phase shift in hepatic protein synthesis in this research. While the previous study indicated that ESR was negatively correlated with plasma zinc concentration at the baseline in all patients ($r = -0.66$, $p<0.0001$) which maintained till six months of follow ups.[26]

Conclusion

The significant positive impact of zinc and vitamin A supplementation on individuals with PTB, particularly in the initial two months of treatment. These findings suggest a potential avenue for refining PTB treatment regimens by incorporating micronutrient supplements, leading to improved clinical outcomes and potential cost-effectiveness. The accelerated conversion of positive sputum smears and earlier radiologic resolution in the supplemented group underscore the potential roles of vitamin A and zinc in enhancing treatment efficacy. Our comprehensive approach, encompassing clinical, radiological, and biochemical parameters, provides valuable insights for personalized interventions in the global effort against tuberculosis.

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