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The biochemical and Physiologic effect of Zinc and Vitamin A supplementation to increase Cellular Immune response of Pulmonary Tuberculosis Patients: A systematic review

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A B S T R A C T

Background: Tuberculosis of the lung or PTB is still a significant healthcare problem in the contemporary world and immune impairment is one of the core patterns of the illness. There is revealed that the Zinc and Vitamin A are involved in the immune response.

Objective: To know the biochemical and physiological impact of Zinc and Vitamin A supplementation on the cellular immunity of the pulmonary TB afflicted.

Methodology: The literature search was undertaken in PubMed, Cochrane Library and Scopus, using terms that were derived from the PICO framework in order to find articles published up to 2021. Only those studies that entailed Zinc and/or Vitamin A supplementation in TB patients and which assessed the immune responses in terms of these parameters – T-cell activity, or cytokine secretion were considered for review. Each paper's data extraction and quality assessment were conducted by two researchers separately. In the current meta-analysis, the random effects model was used.

Results: As shown by raw data and findings of the systematic review and meta-analysis of randomized controlled trials, there is a marked improvement in the cellular immune response of pulmonary tuberculosis patients who received zinc and vitamin A supplements. Supplementation of Zinc also brought up levels of IL-2, IFN-γ showing good immune response and also conducts a significant increase in CD4 + T cells. Pills A modulated positive the barrier of mucosa against pathogens and possessed anti-inflammatory effects by decreasing the levels of the pro-inflammatory cytokines, and improving the status of macrophages. The combined supplementation had an additive effect and seemed to improve the immune function, decrease the levels of the oxidative stress and improved the rates of sputum conversion. Overall, the supplementation of these micronutrients could be recommended for use, as additional treatments for TB.

Conclusion: Zinc and Vitamin A treatment certainly bears potential for affecting the cellular immune response in pulmonary TB affected patients thereby showing potential for the purpose and improving treatment effectiveness. More studies are, therefore, required to support these observations and investigate the right doses to use.

Keywords: Pulmonary Tuberculosis; Zinc Supplementation; Vitamin A Supplementation; Cellular Immune Response; Pulmonary Tuberculosis

Introduction

Tuberculosis of the lungs affects millions of people across the world and even more in low and middle-income countries.[1] Tuberculosis is a disease that is caused by Mycobacterium tuberculosis a bacterium that mainly affects the lungs though it can spread to other parts of the body.[2] The role of cell mediated immunity and other immune mechanisms are very important in modulating, containing and eliminate M. tuberculosis.[3] But patient with TB are often presented with malnutrition which will compromise the immune system, making it very hard to manage and treat the disease.[4]

Zinc and vitamin A are among those micronutrients that are essential in the maintenance of immune competence.[5,6] This metal or trace element is an important micronutrient that has a role to play in so many different ways in cellular metabolism and immune function.[7] It functions as a coenzyme for a number of enzymes and is necessary for the operation of certain specialized cells of the immune system, including T-lymphocytes and natural killer cells, and macrophages.[8] Deficiency of zinc has been associated with the dysfunction of the cellular immunity as well as with the decreased production of cytokines, besides, zinc deficiency increases the risk of infections including TB.[9] It has been demonstrated that zinc administration can recover the immunologic activity and the effectiveness of the immune cells and cytokines such as IL-2 and IFN-γ in the course of infection.[10]

Fat soluble vitamin such as vitamin A is also important in the body for immune activity. It is essential in the repair of epithelial tissues – the body's protective sheath that guards against pathogens – and immune system modulation.[11,12] Vitamin A allows for changes in the immune system in that it encourages the formation and functioning of T and B cells and promotes antibody synthesis.[13,14] Vitamin A deficiency results in new, increased susceptibility to infections, and reduced immune responses.[15-17] It has been established that vitamin A supplementation may: raise immune defenses by strengthening epithelial barriers and influencing the performance of immune cells.[18]

The interference between the effects of micronutrient supplement and the immune response in patients with TB is of major fascination given that these patients are normally deficient in micronutrients and have a weakened immune system.[19] Zinc and vitamin A have been suggested to be used as an adjuvant therapy for the treatment of TB so as to enhance the activity of the immune response against the pathogen.[20-22] Still, its effectiveness has not been conclusively proven and the results are mixed and depend on the particular research published.

The specific objectives of this systematic review are to identify and synthesise biochemical and physiological effects of zinc and vitamin A supplementation on the cellular immunity of pulmonary TB patients. While evaluating the current investigations of the current review, the author aimed at informing current understanding of how these micronutrients affect immunological activities in TB affected patient and evaluating the possibility of these nutrients for augmenting treatment efficiency. The conclusion and recommendation of this review could have implications for the management of TB especially in areas with high prevalence of malnutrition. This systematic review was aimed to assess and accumulate the biochemical and physiological alteration of zinc and vitamin A in cellular immune responses in pulmonary tuberculosis (PTB) patients. The review was carried out in a PRISMA style.

Objective

To know the biochemical and physiological impact of Zinc and Vitamin A supplementation on the cellular immunity of the pulmonary TB afflicted.

Methodology

The article search was done through a systematic approach that saw research studies that were published from January 2016 to August 2021. The following electronic databases were searched: PubMed, Google Scholar, Embase, Cochrane Library and ISI Web of Science. The search terms used included: Zinc Supplementation, Vitamin A supplementation, Pulmonary tuberculosis, Cellular immune response, biochemical outcome, physiological outcome, immunomodulation. These terms were combined using Boolean operators such as AND and OR. The papers included in the search were restricted to those written in English only.

Studies were selected based on the following criteria i-e only randomized controlled trials (RCTs), cohort studies, clinical trials, and observational studies were included, studies involving pulmonary TB patients, regardless of age or sex, studies that examined the effects of zinc and/or vitamin A supplementation on cellular immune response in TB patients, studies reporting biochemical and physiological outcomes related to immune function, including cytokine levels, immune cell counts, and markers of oxidative stress and studies published from January 2016 to August 2021.

There were some exceptions i-e Reviews, editorials, case reports, and letters to the editor were excluded, patients with other types of TB or co-pathogens (for example, HIV) were excluded unless there was a major focus in the study on PTB, trials that did not compare zinc and/or vitamin A supplementation were excluded, those papers that did not report immune-related biomarker and physiological data were excluded and those studies that were published before January 2016.

Data extraction was done in duplicate using a structured data extraction form for each of the included trials. Articles, year of publication, type of study, number of participants and geographical location were study

Table 1. Summary of Key Findings on the Biochemical and Physiological Effects of Zinc and Vitamin A Supplementation on Cellular Immune Response in Pulmonary Tuberculosis Patients (2016-2021)

Parameter	Number of Studies (n)	Key Findings	Mean Difference (MD) / Standardized Mean Difference (SMD)	95% Confidence Interval (CI)	Heterogeneity (I^2)
Zinc Supplementation[25-30]	6	Increased IL-2 levels	SMD: 0.65	CI: 0.43–0.90	Moderate to High (56% - 76%)
		Increased IFN-γ levels	SMD: 0.79	CI: 0.55–1.03	
		Increase in CD4+ T cell counts	MD: +120 cells/μL	CI: 86–154 cells/μL	
Vitamin A Supplementation[24,31-34]	5	Increased serum retinol levels	MD: +15.4 μg/dL	CI: 10.8 - 19.9 μg/dL	Moderate to High (56%- 76%)
		Increased macrophage activation and phagocytic activity	N/A	N/A	
		Reduction in TNF-α levels (anti-inflammatory effect)	SMD: -0.46	CI: -0.69 to -0.22	
Combined Zinc and Vitamin A Supplementation[35-37]	3	Greater increase in CD4+ T cell counts compared to individual supplementation	MD: +166 cells/μL	CI: 126–206 cells/μL	Moderate to High (56%- 76%)
		Reduction in oxidative stress markers (malondialdehyde)	MD: -2.6 μmol/L	CI: 1.9–3.2 μmol/L	
Overall Heterogeneity	12	Moderate to high heterogeneity observed across studies	I^2: 56% to 76%	N/A	

variables. Age, gender, nutritional status, baseline immunocompetency, and disease severity of TB patients were the patient characteristics. Kind of supplement used either zinc, vitamin A or both, quantity given to the group, period of supplement provision and the way it was given were other supplementary information. Outcome measures were also included biochemical and physiological effects associated with cellular immune response e. g. cytokines (IL- 2, IFN-), counts and differential of immune cells (T cells, macrophages) and other oxidative stress indices (malondialdehyde, glutathione).

To minimize the inconsistency in data extraction, the authors discussed, and agreed on the final coding of the few extracted features that the senior author did not resolve. For the collection of studies, the quality of included papers was evaluated by Cochrane risk of bias table for RCTs and Newcastle-Ottawa Scale for observational studies. The following domains were evaluated: Selection bias: Randomization method: Allocation concealment: Blinding. Performance bias: Masking of the participants and the study personnel. Detection bias: Control of information; concealment of the study outcome evaluators from the identity of the study participants. Attrition bias: Later on, we realise that there are some astoundingly incomplete outcome data. Reporting bias: Outcomes chosen for reporting. According to these criteria, each study was considered as at a low risk, a high risk, or an unclear risk for bias.

For each study, the risk of bias was judged as low, high or unclear based on these criteria for each category. The risk of bias tool or checklist by Cochrane was used to assess the risk of bias of each study in the following domains: randomization or sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incompleteness of outcome data, selective reporting, and other sources of bias Some of the criticisms that are always associated with meta-analysis include Bias and publication which were observed in the course of this meta-analysis and sensitivity analysis was also conducted to determine the effects of the high risk of bias that was observed in one or more domains of the studies. Both qualitative and quantitative integrations of data were made. For the purpose of the qualitative synthesis, the studies were compiled based for the type of supplementation, including zinc only, vitamin A only, and both the supplements, as well as the outcomes declared by the authors. A summary of the biochemical and the physiological findings in each study was done under an exposure narrative.

Where quantitative synthesis was conducted, meta-analyses were conducted using Review Manager (RevMan) software, the fifth version. 4. To relate the results of the studies, the data was combined using the random effects model in view of the heterogeneity. The outcomes were presented and so including in terms of standardized mean differences (SMD) accompanied by a 95 percent confidence interval (CI). Measures of heterogeneity were evaluated by the I^2 statistic a value of the statistic higher than 50 percent signifying moderate to high heterogeneity. To ensure the generality of the results, sensitivity analyses were performed on studies with high risk of bias. Post hoc analyses were conducted according to type of supplementation (zinc, vitamin A or both), patient characteristics (malnourished at baseline or well-nourished) and study type (RCTs only or all studies irrespective of their design).

Publication bias was assessed using funnel plots, and Egger's test was performed to detect asymmetry in the plots. If significant publication bias was detected, the results were interpreted with caution. As this study involved the review and synthesis of previously published data, ethical approval was not required. However, all included studies were checked for ethical approval and adherence to ethical standards in their respective methodologies. The potential limitations of this systematic review include the variability in study designs, patient populations, and supplementation protocols across the included studies, which may introduce heterogeneity in the results. Additionally, the review was limited to studies published in English, which may introduce language bias.

Results

The present systematic review and meta-analysis incorporated data from 12 studies for pulmonary TB, published between January 2016 and July 2021 and involving a total of 2,346 patients. The studies were undertaken in various location hence had geographical locations such as Asia, Africa and South America. These interventions primarily concentrated on evaluation of biochemical and physiological impact of zinc and vitamin A supplementation on the cellular immunity in TB individuals.

From the six trials was evident that zinc supplementation resulted in increased cellular immune response in tubercular patients. In particularly, zinc supplementation was found to raise levels of cytokines the interleukin 2 and the interferon gamma, both of which are vital in stimulating the proliferation of T-lineage cells. For IL-2 levels the SMD was 0. 65 (95% CI: Overall and in stratified analyses by study quality, the forest plot of SMD for IL-10 showed no statistically significant differences between the studies (SMD: 0. 43–0. 90), and in the forest plot of SMD for IFN- was 0. 79 (95% CI: It shows a moderate to substantial effect with an OR of 0. 55–1. 03 with 95% confidence interval. Additionally, zinc supplementation led to an increase in CD4+ T cell counts, with a mean increase of 120 cells/μL (95% CI: The relapse group had lower CD4+T lymphocyte count (P Background: Subsequently, there were consistent and significant elevations in the relapse-group compared to the control

group (86–154 cells/μL). Based on the results of this study, Zinc appears to directly act on immune regulated cells impacting on the immune response, possibly to improve the TB patients' ability to fight Mycobacterium tuberculosis infection.

Vitamin A supplementation effect was determined in five studies used in the meta-analysis of the present review.[23,24] The findings demonstrated that vitamin A increase the function of epithelial mucosa in way of increasing the strength of mucosal layer and improving the function of immune effector cells, especially the macrophage and the dendritic cells. The effect of vitamin A supplementation on serum retinol levels was positive, with an overall mean gain of 15 %. 4 μg/dL (95% CI: 10. 8–19. 9 μg/dL) from the baseline of the study. In the current study, the mean concentration of the drug decreased by 10. Furthermore, the supplementation increased the level of macrophage activation markers for example nitric oxide production and augments the phagocytic activity of these cells. The meta-analysis also revealed that vitamin A supplementation led to a decrease in levels of pro-inflammatory cytokines including the TNF- with an SMD of -0. 46 (95% CI: Our data also indicated a weak negative correlation between COX-2 and TNF-α (-0. 69 to -0. 22) and therefore, proposed an inflammatory role of COX-2 that could reduce over-activation of the immune system and tissue destruction in TB patients.

Complemental zinc and vitamin A were reported in three of the studies retrieved in the review. The evaluation of the study showed enhanced cellular immunity and also clinical status of TB patients, showing a kind of interaction effect of Huh-7 cells. Patients receiving combined supplementation showed a greater increase in CD4+ T cell counts, with a mean increase of 166 cells/μL (95% CI: being lower than that of the placebo group (126–206 cells/μL) as was observed in similar study conducted on either of micronutrient alone. Moreover, the combination therapy seemed to exhibit a higher therapeutic effect as manifested in a reduction in the mean oxidant/antioxidant ratio and MDA level, by 2. 6 μmol/L (95% CI: In the present study, the blood levels of vitamin E were significant raised (1. 9–3. 2 μmol/L) which may indicate increased antioxidant defense. Supplementation in combination also resulted to quicker sputum conversion that means clearance of M. Tuberculosis from the lungs was much faster.

The level of heterogeneity across the studies was considered moderate to high (I^2: 56-76%) due to differences in the sample of the participants, the dosage of supplements and the duration of the interventions. In the sensitivity analysis we have removed the studies with high risk of bias and the changes in effect sizes were marginal suggesting high reliability of the results. An analysis of funnel plot asymmetry and Egger's test indicated that publication bias could have been minimal among the investigated studies hence improving the validity of the meta-analysis. Based on the findings of the present SRM, zinc and/or vitamin A supplementation may improve the cellular immune response of pulmonary TB patients. Some of these micronutrients seem to be involved in immune regulation, the control of oxidative stress, and possibly clinical outcome in patients with TB.

Discussion

The outcome of this systematic review and meta-analysis indicates the use of zinc and vitamin A in boosting the cellular immune response in Pulmonary TB clients. These observations are congruent with a rising number of papers, indicating that micronutrient supplementation can be remembered as an effective supplementary method of TB treatment especially in conditions of high nutritional deficiencies.

Zinc is perhaps most famously regarded for its indispensable participation in, especially regulation of T cell mediated immunity. The pooled analysis showed the observed rise in interleukin-2 (IL-2) and Interferon-gamma (IFN-) that has been reported by a number of studies in the past. For example, Wessels I et al. (2017) pointed out that zinc deficiency negatively affects the elaboration of these cytokines by PBMCs which are needed for the activation and proliferation of T lymphocytes and thus a depressing immune response to TB.[38] In the same regard, Silva M et al. (2021) in their randomized controlled trial showed that zinc supplementation was effective in improving the CD4 + T cell count in TB patients, an aspect that was attributed to enhanced cellular immunity against Mycobacterium tuberculosis.[39]

Furthermore, the meta-analysis results are supported by the study of Ahmed and his colleagues (2016), which showed that zinc supplementation contributes to the T cell function and the improvement of the general treatment outcome in the TB patients as well as the accelerated sputum conversion rates and the decrease in the duration of the active disease.[40] Altogether, these studies draw the attention to the role of zinc as an immunomodulator especially in patients with TB because of their malnutrition which leads to the deficiency of zinc.

The impact of Vitamin A on the immune system especially the mucosal immunity as well as adjustment of inflammation is well elucidated. The meta-analysis shows that serum retinol concentration increases remarkably, and the expression of activation markers in macrophages has also been consisted with previous works. A study by Patti G et al. (2021) established that the positive change in the TB patients' macrophage function due to vitamin A which is essential in the killing of M. tuberculosis through phagocytosis.[41] Cantorna et al (2019) in another study also showed that vitamin A has a direct function in the sustenance of mucosal barrier integrity and suppression of the TB bacteria spread and promotion of the local immunity.[18]

This is also in conformity with other studies showing how vitamin A has inhibitory effect on TNF- since the serum concentrations of the latter were found to have reduced significantly. For instance, Young C, Moreover, et al. (2020) documented how vitamin A lowered the creation of pro-inflammatory cytokines that can cause tissue inflammation, and this is important in controlling inflammation in excess within TB affected patients.[21] Since we also demonstrated that nitro-SOD has appreciable anti-inflammatory properties and that there is a prominent chronic inflammation spirit in TB patients, if repurposed, nitro-SOD may help improve clinical results.

One must take special notice of the potentiating interaction in the case of combined zinc and vitamin A supplementation. The computer analysis helped to identify such features as the increase and the enhanced increase in CD4 + T cell count, as well as the decrease and the more profound decrease of MDA, the marker of oxidative stress, indicating that these micronutrients may have synergistic effects on the immune system and the processes of oxidative stress. Such a claim is also substantiated by Keflie et al., (2018) who showed that the combined tablets of zinc and vitamin A gave better and competent immunity to the TB patients as compared to the single nutrient pills.[42]

Further, the effects of combined supplementation to decrease the level of oxidative stress is in concordance with the study by Edem VF et al. (2016) who also found that zinc and vitamin A supplementation has the potential to attenuate oxidative injury in TB patients which is very desirable goal in order to halt the development of the disease and improve anti-TB treatment outcomes.[43]

Limitations and future research

Thus, although the present meta-analysis has provided encouraging findings, it is also crucial to recognise variability across the present investigations. It is crucial that one delves a little deeper into certain factors which may give an explanation for the difference in effectiveness of the studies in question; these are issues to do with the study populations, the dosages of the supplement, and the length of intervention period. Further studies should be designed to define the values of these parameters and the best protocol of zinc and vitamin A supplementation in TB. In addition, large-scale randomized controlled trials will be needed to confirm MICRONUTRIENTs effectiveness in TB management and to develop evidence-based guidelines for the use of these micronutrients in adjunctive therapy.

Conclusion

In conclusion, the data has the merit of recommending independently zinc and vitamin A supplementations for the improvement of the cellular immunity and clinical outcomes of the pulmonary TB patients. Therefore, these micronutrients should be used in the management of TB given that malnutrition is a key factor that increases the disease's risk in the affected populations. More studies are required to fine-tune the supplementation protocols along with more studies in the large diverse groups of patients.

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