RESEARCH ARTICLE

Adjunct Therapy of Zinc Supplementation Increases Immunological Response in HIV-Infected Patients: A Systematic Review and Meta-Analysis

Dwijo Anargha Sindhughosa¹, I Ketut Agus Somsia²*, Ketut Tuti Parwati Merati¹ and Ketut Suryana³

¹Internal Medicine Residency Program, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia
²Department of Internal Medicine, Tropical and Infectious Disease Division, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia
³Department of Internal Medicine, Immunology Division, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia

Abstract:

Introduction:

Malnutrition greatly accelerates the impairment of immune function among HIV-infected patients. Zinc deficiency is often found in people living with HIV/AIDS, affecting their immune function. Several studies have evaluated the effect of zinc in HIV-infected patients, including CD4 T-cells. However, the results have varied. This review aimed to evaluate the effect of zinc supplementation in HIV patients, particularly its effect on CD4 T-cells count.

Methods:

Relevant publications were obtained from PubMed database, Google Scholar, COCHRANE, and Science Direct. The primary outcome was CD4 T-cells count, while the secondary outcomes were viral load and zinc levels. Year of publication, type of study, population, doses of zinc given, duration of zinc administration, sample size, age, and baseline CD4 T-cells counts were also obtained and reported. Quantitative data from the publications were analyzed using a fixed-effect model or a random-effect model.

Results:

We evaluated 13 full-text articles on zinc supplementation in HIV-infected patients, involving 802 subjects for the experiment group and 742 subjects for the control group. Overall, zinc supplementation, whether as zinc supplementation-only or prepared as multiple micronutrient or multivitamin preparation, increases CD4 T-cells counts by 33.14 cells/mm³ (p = 0.02; 95% CI: 6.09 to 60.19), irrespective of age. Subgroup analysis revealed CD4 T-cells counts also increase in patients who receive zinc supplementation-only preparation by 33.56 cells/mm³ (p = 0.04; 95% CI: 1.5 to 65.63). Zinc supplementation increases serum zinc levels with pooled mean difference of 15.41 µg/dl (p < 0.05; 95% CI: 12.77 to 18.06). However, the viral load did not significantly decrease with zinc supplementation, with a pooled mean difference of -4.02 copies/ml (p = 0.7; 95% CI: -24.78 to 16.75), based on the random-effect model.

Conclusion:

Zinc supplementation in HIV-infected patients enhances immunological response, characterized by an increase in CD4 T-cells counts. In addition, it increases zinc serum levels in HIV-infected patients, indicating the importance of zinc supplementation in this group of patients.

Keywords: Zinc supplementation, HIV-infected patients, CD4 T-cells, Immunological response, Viral load, Peptides.

1. INTRODUCTION

Human Immunodeficiency Virus (HIV) is a retrovirus that primarily targets CD4 T-cells and macrophages, subsequently leading to the suppression of CD4 T-cells [1]. T cells are a key factor in reducing the impact of HIV infection; hence, their performance is greatly needed [2]. CD4 T-cells can also be used as a severity indicator. CD4 or CD8 T-cells recognize viral antigenic peptides and may trigger various cytokines, e.g., interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-β (TNF-β), subsequently triggering the multicellular immune response. Therefore, the lack of CD4 T-cells as a consequence of HIV infection results in a decrement of CD8
T-cells and cytokines [3].

Malnutrition remains a major concern for the adequate management of HIV-infected patients. It has been known that malnutrition accelerates the progression of HIV to acquired immune deficiency syndrome (AIDS). The condition is associated with the food adequacy of patients because it affects the ability to acquire, consume, and utilize food [4]. Studies have evaluated the epidemiological aspect of malnutrition in people living with HIV/AIDS. One study conducted in Brazil evaluated malnutrition prevalence in the 20-59 years old group. In the study involving 127 patients, malnutrition was found in 55 (43%) patients, defined by BMI < 18.5 kg/m². A total of 15% were in a severe malnutrition state, indicated by a BMI of < 16 kg/m² [5].

The magnitude of malnutrition in HIV-infected patients affects HIV-infected patients’ mortality and morbidity rate. The effect of malnutrition on mortality and morbidity is supported by the Nutrition for Healthy Living (NFHL) study. The risk of death increases by 11% for every 1% increase in weight loss since the previous visit. The risk might increase sixfold if weight loss was >10% below the baseline weight [6].

Malnutrition conditions affect susceptibility to infection by altering the immune system in various possible ways. The weakened immune status results in an increment of HIV replication, consequently accelerating HIV progression to AIDS. Furthermore, untreated patients with HIV/AIDS are at risk for malnutrition. A similar outcome also happens in infants and children (less than five years old) [7, 8].

Among the malnutrition in HIV-infected patients, zinc deficiency is often found. It may be associated with a decrease in immunity to maintain the body’s immune systems. A study by Baum et al. [9] reported zinc deficiency occurs in HIV-infected adults reached >50%. The result is consistent with the study by Asemota et al. [10], which found that 56% of 100 HIV patients had zinc deficiency.

The impact of zinc deficiency includes the detain in the metabolism of nutrients. A low level of zinc in plasma may reduce the sensitivity of the immune system to various infections. It also weakens the activity of phagocytosis and the production of cytokines [11]. Inadequate amounts of cytokines, primarily T helper (Th) cells, interferon (IFN), and leukocytes together with B lymphocytes, may alleviate pathogens invading the body’s immune system.

Various randomized controlled trials (RCTs) have investigated the effect of zinc supplementation on HIV patients [12 - 24]. The outcomes included: CD4+ T-cells counts, viral load, neuropathy, diarrhea, and death. Considering the effect of zinc supplementation toward CD4+ T-cells counts, varying results were obtained. To the authors’ knowledge, only three studies closest to the meta-analysis of zinc supplementation toward CD4+ T-cells counts in HIV-infected patients were available. Zeng et al. [25] conducted a systematic review in 2011 on the effects of zinc supplementation in adult patients, children, and pregnant women. However, the meta-analysis that specifically analyzes zinc’s effect on CD4+ T-cells counts only included three studies. Furthermore, there are ten years of gap to date, and other RCTs have been carried out with various results obtained. Kayode and Anaba [26] conducted a systematic review study regarding vitamin D, selenium, or zinc supplementation in patients with HIV. They discussed the effect of zinc on various outcomes in HIV-infected patients, e.g., CD4+ T-cells, diarrhea morbidity, zinc levels, and others. However, no meta-analysis was done. Jiang et al. [27] conducted a meta-analysis but focused on micronutrient supplementation; the study did not specifically address zinc and involved only six studies without evaluating CD4+ T-cells counts. Therefore, further studies are needed to evaluate the effect of zinc supplementation in HIV patients, especially its effect on CD4+ T-cells cell count. This review aimed to evaluate the effect of adjunct therapy of zinc supplementation on the immunological response of HIV-infected patients, characterized by the change in CD4+ T-cells count.

2. MATERIALS AND METHODS

2.1. Literature Search

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines were followed for conducting and reporting meta-analysis data. The eligibility criteria were decided by implementing the patient, intervention, comparison, and outcome (PICO) concept. The framework of PICO used for this study is depicted in Table 1. The eligibility criteria (PICO) were extracted into keywords utilizing the Boolean operator. In this study, we used keywords (HIV OR human immunodeficiency virus) AND (zinc) AND (CD4 OR Cluster of differentiation 4) AND (RCT OR Randomized controlled trial) in PubMed database, Google Scholar, COCHRANE, and Science Direct as a search engine to find eligible journals. As for Google Scholar, we screen the first 200 relevant articles from a total of 21,700 articles [28]. We also evaluate the references of the relevant articles. The last search was run on May 7th, 2021.

2.2. Study Selection

The study selection process was conducted by three authors (DAS, IKAS, KS) to minimize the likelihood of ruling out potentially relevant studies. When disagreement took place, the decision of the first, second and third authors was considered. Study selection started with disposing of duplicate records. Title and abstract screening were performed to exclude irrelevant studies. Subsequently, studies that passed the first evaluation were further assessed to evaluate their compliance with the inclusion and exclusion criteria for this review. All studies included were thoroughly evaluated for their quality before eventually being included by implementing the critical appraisal tool of Cochrane Collaboration’s risk-of-bias method [29].

The current systematic review and meta-analysis included all studies prior to May 7th 2021, with full-text available, evaluating the additional administration of zinc in HIV-infected patients. Article with the type of case report, qualitative and economic studies, review, cadaveric and anatomic was excluded from the current study. All articles that did not provide the required data for conducting a meta-analysis were also excluded. To prevent duplication, articles written by the same author within the same institution were evaluated for the subjects.
The primary outcome investigated in the current systematic review and meta-analysis was the CD4 T-cells count (cells/mm$^3$) as the immunological response. The secondary outcome included viral load (copies/ml) and zinc serum level (µg/dl). All authors used an electronic data collection form to collect the required data from each article. The data was then combined and managed with software Review Manager 5.4.

The data items were the author’s name, year of publication, type of study, population, doses of zinc given, duration of zinc administration, sample size, age, and baseline CD4 T-cells counts. The mean difference of CD4 T-cells, viral load, and zinc serum level after and before administration of zinc in both treatment and control groups were performed the meta-analysis.

2.4. Risk of Bias

A standardized critical appraisal tool was utilized to ensure the quality of all articles that complied with the eligibility criteria for this review. This process, which aimed to minimize the likelihood of bias in study selection, was performed independently by two authors (DAS and KTPM). The critical appraisal tool employed for this review was Cochrane Collaboration’s risk-of-bias method [29].

2.5. Statistical Analysis

The mean difference of CD4 T-cell counts in HIV-infected patients with zinc supplementation and without zinc supplementation were pooled and analyzed, along with the funnel plot. The analysis was also done as subgroups, stratified by age (adult and children) or zinc preparation (zinc supplementation only and received zinc as multiple micronutrient or multivitamin preparation). If data were presented as median with Q1 and Q3, the mean was calculated using a calculator, along with standard deviation (SD) and standard error (SE). We also combined two treatment groups in a specific article into one group, according to its allocation (treatment or control), by using the calculator. Heterogeneity was analyzed with Tau$^2$, Chi$^2$ or I$^2$. The fixed-effect model (FEM) or random effect model (REM) was used accordingly. Meta-analysis was performed with software Review Manager 5.4.

3. RESULTS

3.1. Study Selection

By utilizing the foremost search strategy, we found a total of 250 studies from database searching and no additional records identified through other sources. After the duplicates were removed, we obtained 214 articles. We excluded 182 articles by screening the titles and abstracts, leaving us 32 relevant studies. Studies that did not provide all the information needed for this meta-analysis, a report from the same study, and studies in which the comparator group without zinc was not available were excluded. Screening and qualitative evaluation were performed; then, we obtained 13 articles used for the current systematic review and meta-analysis. PRISMA study flow diagram is depicted in Fig. (1).

3.2. Study Characteristics

We included 13 full-text articles on zinc supplementation in HIV-infected patients. The publication year of these articles varied from 1995 to 2021, with a total of 802 subjects for the experiment group and 742 subjects for the control group. The experiment group received zinc supplementation in varying doses and duration. All patients in the studies included were in antiretroviral treatment, except for the study by Esiovwa et al. [12], Freiberg et al. [14], and Jiamton et al. [23]. However, the majority (94.7%) of the subjects in the study by Esiovwa et al. [12] were on highly active antiretroviral therapy (HAART). In the study by Freiberg et al. [14], no important differences in ART initiation occurred between the experiment and control group. As for the study by Jiamton et al. [23], only 10 participants of the total participants were taking antiretroviral (five in the experiment group and five in the control group; the total participants in the experiment group were 192 subjects and the control group had 184 subjects). The summary of findings and studies characteristics is depicted in Table 2.

### Table 1. PICO framework of the study

| Patient | Human immunodeficiency virus |
|---------|-----------------------------|
| Intervention | Zinc supplementation |
| Comparator | Placebo |
| Outcome | CD4 T-cells |

Zinc in HIV Patients
Fig. (1). PRISMA flow diagram of the study.

Table 2. Summary of findings and studies characteristics.

| Author          | Type of Study                       | population                        | Zinc intervention and comparator                               | Duration | Sample Size, experiment vs. control | Age, experiment vs. control | Baseline CD4 T-cells, experiment vs. control |
|-----------------|-------------------------------------|-----------------------------------|----------------------------------------------------------------|----------|-------------------------------------|-----------------------------|---------------------------------------------|
| Esiovwa et al.  | Double-blind, randomized controlled study | HIV-positive children, aged 5-12 years | Experiment: multivitamin with zinc 5 mg. Control: multivitamin without zinc | 6 months | 126 subjects vs. 64 subjects        | 7.75 ± 1.94 and 8.08 ± 1.94 vs. 8.08 ± 1.99 years old | 971.27 ± 541.17 vs. 975.44 ± 453.07 cells/µL |
| Author | Type of Study | population | Zinc intervention and comparator | Duration | Sample Size, experiment vs control | Age, experiment vs control | Baseline CD4 T-cells, experiment vs control |
|--------|---------------|------------|-----------------------------------|----------|------------------------------------|--------------------------|--------------------------------------|
| Silva et al. (2021) [13] | Two-stage of study. The first stage is case and controls, paired by age and sex in a 1:1 ratio. The second stage is randomized patients to receive intervention versus a placebo | Confirmed HIV with immunovirological discordance (IVD) patients | Zinc sulfate at a dose of 15 mg/day versus placebo | 12 months | 19 subjects vs 21 subjects | 46.0 (40.0-54.0) vs 48 (44-55.0) years old* | 197 (177-216) vs. 180 (131-198) cells/mm³* |
| Freiberg et al. (2020) [14] | double-blinded placebo-controlled randomized clinical trial | HIV-infected patients | Experiment: zinc gluconate capsule and 50 mg of riboflavin (adherence measure). Men: 15 mg of elemental zinc gluconate and women: 12 mg daily by mouth | 18 months | 126 subjects vs 128 subjects | 34 ± 5 vs. 34 ± 6 years old | 511 ± 296 vs 530 ± 288 |
| Hadadi et al. (2020) [15] | Randomized double-blind placebo-controlled trial | Adult patients (18 and 60 years) with confirmed HIV-1 infection, who were receiving combination antiretroviral therapy (CART) | Experiment: 220 mg zinc sulfate capsules (= 50 mg of elemental Zn) once daily (before lunch). Control: placebo capsules | 6 months | 49 subjects vs 44 subjects | 38.1 (8.8) vs 38.6 (8.8)* | 316 (±66) vs 312 (±68) cells/mm³* |
| Contreras-Martinez et al. (2017) [16] | A double-blind, randomized, placebo-controlled clinical trial | HIV-infected patients | Experiment: A daily dose of 20 mg of zinc sulfate. Control: placebo | 12 weeks | 20 subjects vs 20 subjects | 50.2 ± 9.7 vs 48.7 ± 9.4 years old | 157 (86.75) vs control: 163 (56)* |
| Lodha et al. (2014) [17] | Randomized, double-blind, placebo-controlled trial | All HIV-1-infected children older than 6 months in whom initiation of ART was indicated as per the guidelines | Experiment: 20 mg of elemental zinc as sulfate daily for 24 weeks Control: Placebo. Both groups received 1 recommended dietary allowance (RDA) of multivitamins everyday | 24 weeks | 25 subjects vs 24 subjects | Mean (SD): 80.4 ± 43.6 vs 86.6 ± 50.6 months | 412.5 (196.5-645) vs 392.5 (269.25-874.25) cells/µL |
| Asdamongkol et al. (2013) [18] | A pilot clinical study of two phases; phase one was a cross-sectional study, and phase two was a prospective, randomized, placebo-controlled clinical trial | HIV-infected patients with immunological discordance | Experiment: Daily zinc supplementation consisted of 15 mg of chelated zinc. Control: Placebo | Six months | 13 subjects vs 17 subjects | 45.0 ± 11.0 years old in total. No data for intervention and control group | 183 (151-213) vs 162 (139-182) cells/mm³* |
| Rahafiludin et al. (2013) [19] | Experimental study with pre-test post-test with control group design | HIV-infected patients | Experiment: Zinc supplementation 5mg/day, along with AZT. Control: Only AZT | One months | 10 subjects vs 10 subjects | Not clear | 371.3 ± 126.8 vs 396.3 ± 257.9 cells/µL |
response in HIV-infected patients by increasing CD4+ T-cells counts. Based on random effect model ($I^2=79\%$; $\chi^2 = 58.04; p < 0.00001$), pooled mean difference of CD4 T-cells counts between zinc supplementation and without zinc supplementation was 33.14 cells/mm$^3$ ($p =0.02; 95\% CI: 6.09$ to $60.19$) (Fig. 3), indicating that zinc supplementation increases CD4+ T-cells counts significantly by 33.14 cells/mm$^3$. Even though subgroup analysis according to age did not find that zinc supplementation significantly increases CD4+ T-cells counts ($p = 0.05$ for adults and $p = 0.25$ for children), pooled analysis found a significant increase of CD4+ T-cells in zinc treated group. Funnel plot analysis is depicted in Fig. (4).
Fig. (2). Risk of bias in all included studies.
Fig. (3). Effect of zinc supplementation on CD4+ T-cells levels subgroup by age.

Fig. (4). Funnel plot of zinc supplementation to CD4+ T-cells levels subgroup by age.

To determine whether the effect of the increase in CD4+ T-cells counts was due to other effects of micronutrients/multivitamins or not, we subgrouped the analysis according to the intervention given (zinc supplementation only or receiving zinc as multiple micronutrient or multivitamin preparation). According to
subgroup analysis, CD4+ T-cells counts also increase in patients who receive zinc supplementation only by preparation by 33.56 cells/mm³ (p = 0.04; 95% CI: 1.5 to 65.63), with random effect model analysis (Fig. 5). Funnel plot analysis is depicted in (Fig. 6).

3.5. Effect of Zinc Supplementation on Viral Load and Serum Zinc Level of HIV-Infected Patients

The pooled mean difference of viral load, which included three studies, after zinc supplementation was -4.02 copies/ml (p =0.7; 95% CI: -24.78 to 16.75), based on the random effect model (Fig. 7), meaning viral load did not significantly decrease with zinc supplementation. Meanwhile, the effect of zinc supplementation on serum zinc levels showed a significant increase in serum levels. Zinc supplementation increases serum zinc levels with a pooled mean difference of 15.41 µg/dl (p < 0.00001; 95% CI: 12.77 to 18.06) (Fig. 8), based on fixed effect model analysis.

![Fig. (5). Effect of zinc supplementation on CD4+ T-cell levels subgroup by intervention, given as zinc supplementation only or concomitant with other micronutrients or vitamins.](image)

![Fig. (6). Funnel plot of zinc supplementation to CD4+ T-cells levels subgroup by intervention given.](image)
**4. DISCUSSION**

The current meta-analysis highlighted the importance of zinc supplementation in HIV-infected patients. Overall, zinc supplementation, whether as zinc supplementation only or prepared as multiple micronutrient or multivitamin preparation, may improve immunological response in HIV-infected patients by the increase in CD4+ T-cells counts irrespective of age or the preparation. Furthermore, considering the preparation given, zinc supplementation-only preparation also increases CD4+ T-cells count.

The main finding in the current meta-analysis was zinc supplementation increases CD4+ T-cells counts significantly by 33.14 cells/mm$^3$. Considering the fact that the immune system in the body is greatly influenced by zinc deficiency, the increase of CD4+ T-cells in people with HIV/AIDS by the addition of zinc supplementation offers treatment benefits. Immunological failure is one of the criteria for determining treatment failure in people with HIV. It is defined by a fall of CD4 T-cells counts to pretherapy baseline (or below) or a 50% fall from the on-treatment peak value (if known) or persistent CD4 T-cells levels below 100 cells/mm$^3$ six months after ART initiation [30]. Therefore, the CD4+ T-cell count is an issue that every clinician should be wary of. The increase in CD4+ T-cell count by 33.14 cells/mm$^3$ by adding zinc supplementation offers a clinical advantage.

It has been known that other micronutrients and multivitamins also affect the immune system of the body [31]. In order to understand whether the effect of the increase in CD4+ T-cells count is due to other effects of micronutrients/multivitamins or not, this meta-analysis divided the subgroups according to the intervention given. The intervention is divided into zinc supplementation only or receiving zinc as multiple micronutrients or multivitamin preparation. According to subgroup analysis, CD4+ T-cells counts also increase in patients who receive zinc supplementation only preparation.

The exact mechanism of zinc in regulating various processes of immune response is still not completely elucidated. Zinc is a chemo-attractant for several immune cells, and its lack of amount may result in the decrease of polymorphonuclear cells' chemotaxis [32]. A decrease in zinc concentration also hampers phagocytosis; hence its supplementation increases phagocytosis. In the adaptive immune system, zinc deficiency affects T cells, either in the developmental stage or functionally. An inadequate amount of zinc leads to atrophy of thymic and T-cell lymphopenia [33]. Furthermore, zinc is responsible for T-cell activation by stimulating the autophosphorylation of the protein kinase Lck via interaction with the cytoplasmic tails of CD4 and CD8 T-cells [34].

Several RCT studies have been conducted on whether zinc supplementation may improve the outcome in HIV-infected patients, including neuropathy, infection, and death. Considering its effects on CD4+ T-cells counts, varying results were obtained [12 - 24]. However, the studies that specifically analyzed the effect of zinc supplementation on CD4+ T-cell changes are scarce in the literature. Compared to the current study, only three studies closest to the meta-analysis of zinc supplementation toward CD4+ T-cells counts in HIV-infected patients were available. However, the limitations of each study restrict the applicability of the results obtained to the clinical setting. The current study addressed the limitations of the previous studies. A total of 13 articles were included in this study. We subgrouped it according to age (adults and children) and zinc preparation (zinc-only and zinc as micronutrients or multivitamins added) to evaluate its effect specifically for adults or its preparation.

Considering that the increase in CD4+ T-cells cells count was influenced by antiretroviral therapy, we evaluate the use of antiretroviral therapy for this review. Three studies mixed the...
Zinc in HIV Patients

The Open AIDS Journal, 2022, Volume 16

11

SUPPLEMENTAL MATERIAL

PRISMA checklist is available as supplemental material on the publisher’s website along with the published article.

REFERENCES

[1] Doiith G, Greene WC. Dissecting how CD4 T Cells are lost during HIV infection. Cell Host Microbe 2016; 19(3): 280-91. [http://dx.doi.org/10.1016/j.chom.2016.02.012] [PMID: 26962940]

[2] Li JR, Gong RY, Li YP, Bai Y, You F, Deng S. Research on HIV: Toxoplasmogondii co-infection and cytokine levels among intravenous drug users. Parasite Immunol 2010; 32(2): 161-4. [http://dx.doi.org/10.1111/j.1365-3024.2009.01175.x] [PMID: 20070830]

[3] Saddiki N, Kelleher AD. Regulatory T cells in HIV infection: Who’s suppressing what? Curr Infect Dis Rep 2008; 10(3): 252-8. [http://dx.doi.org/10.1007/s11908-008-0041-8] [PMID: 18510889]

[4] Duggal S, Chauj HD, Duggal AK. HIV and malnutrition: Effects on immune system. Clin Dev Immunol 2012; 2012: 1-8. [http://dx.doi.org/10.1155/2012/784740] [PMID: 22242039]

[5] Andrade CS, Jesus RP, Andrade TB, Oliveira NS, Nabby SA, Ribeiro GS. Prevalence and characteristics associated with malnutrition at hospitalization among patients with acquired immunodeficiency syndrome in Brazil. PLoS One 2012; 7(11): e84717. [http://dx.doi.org/10.1371/journal.pone.0084871] [PMID: 23144941]

[6] Mangili A, Murman DH, Zampini AM, Wanke CA, Mayer KH. Nutrition and HIV infection: Review of weight loss and wasting in the era of highly active antiretroviral therapy from the nutrition for healthy living cohort. Clin Infect Dis 2006; 42(6): 836-42. [http://dx.doi.org/10.1086/500398] [PMID: 16477562]

[7] Patel D, Bland R, Coovadia H, Rollins N, Coutoukas A, Newell ML. Breastfeeding, HIV status and weights in South African children: a comparison of HIV-exposed and unexposed children. AIDS 2010; 24(3): 437-45. [http://dx.doi.org/10.1097/QAD.0b013e3283345691] [PMID: 19915445]

[8] Nguefack F, Ehouzou MN, Kamgaing N, et al. Clinical characteristics and outcome of acute severe malnourishment in HIV-infected children: A 5-year retrospective study. J Pediatr Pueric 2015; 28(5): 223-32. [http://dx.doi.org/10.1016/j.jsp.2015.07.002]

[9] Baum MK, Lai S, Sales S, Page JB, Campa A. Randomized, controlled clinical trial of zinc supplementation to prevent immunological failure in HIV-infected adults. Clin Infect Dis 2010; 50(12): 1653-60. [http://dx.doi.org/10.1086/652864] [PMID: 20455705]

[10] Asemota EA, Okafiin JM, Okororowu HU, et al. Zinc, copper, CD4 T-cell count and some hematological parameters of HIV-infected subjects in Southern Nigeria. Integ Med Res 2018; 7(1): 53-60. [http://dx.doi.org/10.1016/j.imr.2018.01.008] [PMID: 29629291]

[11] Sneij A, Campa A, Martinez SS, Stewart T, Baum M. Lower plasma zinc levels in hyperglycemic people living with HIV in the MASH cohort. J AIDS Clin Res 2016; 7(2): 542-51. [http://dx.doi.org/10.4172/2155-6133.1000542] [PMID: 27182454]

[12] Esiovwa R, Rankin J, David A, Diou E, Wapmuk A, Amoo O. The role of multimicronutrient supplementation in pediatric HIV management in Nigeria: A randomized controlled study. J Pediatr Infect Dis Soc 2021; 10(2): 112-7. [http://dx.doi.org/10.1093/jpids/piaa025] [PMID: 32202619]

[13] Silva M, Montes CG, Canals A, Mackenna MJ, Wolff M. Role and effects of zinc supplementation in HIV-infected patients with immunovirological discordance: A randomized, double blind, case control study. PLoS One 2021; 16(11): e024823. [http://dx.doi.org/10.1371/journal.pone.024823] [PMID: 33481813]

[14] Freiberg MS, Cheng DM, Gnatienko N, et al. Effect of zinc supplementation vs placebo on mortality risk and HIV disease progression among HIV-positive adults with heavy alcohol use: A randomized clinical trial. JAMA Netw Open 2020; 3(5): e204330. [http://dx.doi.org/10.1001/jamanetworkopen.2020.4330] [PMID: 32383748]

[15] Hadadi A, Oostvar A, Edelat Noor B, et al. The effect of selenium and zinc on CD4(+) count and opportunistic infections in HIV/AIDS patients: a randomized double blind trial. Acta Clin Belg 2020; 75(3): 170-6. [http://dx.doi.org/10.1080/17843286.2019.1590023] [PMID: 30888253]

subjects with antiretroviral therapy and without antiretroviral therapy [12, 14, 23]. In one study, the majority (94.7%) of the subjects were on highly active antiretroviral therapy (HAART) [12]. Another study showed no important differences in ART initiation between the experiment and control group [14], while in the other study [23], only a small portion of participants was taking antiretroviral (five in the experiment group and five in the control group; the total participant in experiment group was 192 subjects and control group was 184 subjects). Considering those facts, it could be assumed that little or no influence of antiretroviral therapy in CD4+ T-cells count changes in the current meta-analysis.

The current meta-analysis is also subject to limitations. This study focused primarily on CD4+ T-cells counts, even though the secondary outcome also targeted its effect on viral load. A further study analyzed its effect on viral load, and more studies should be performed in the future. Additionally, as a small portion of subjects were distinct in relation to the use of HAART or not, a small likelihood should be considered, as it may affect the outcome of zinc supplementation on CD4+ T-cell count or viral load. Various durations of zinc supplementation, different HAART regimens and durations, and adherence would influence the outcomes. Furthermore, it would also be beneficial to evaluate the effect of zinc supplementation on other parameters, e.g., comorbidity incidence or other opportunistic infections.

CONCLUSION

Zinc supplementation increase CD4+ T-cells counts of HIV-infected patients, irrespective of the age of the patients or the preparation of zinc administered to the patients. It also increases serum zinc levels of HIV-infected patients, indicating the importance of zinc supplementation for HIV-infected patients.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines have been followed.

AVAILABILITY OF DATA AND MATERIALS

The data of the study would be made available by contacting the corresponding author [K.A.S] on reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.
[16] Contreras-Martínez H, Duque-Molina M, Vásquez-Trespalacios EM, Sánchez-Geiré J. Effect of zinc on immune recovery in HIV patients. Medellín 2013. Randomized controlled trial. Ces Medicina 2017; 31(1): 3-13. [http://dx.doi.org/10.2165/cesmedicina.31.1.1]

[17] Lodha R, Shah N, Mohari N, et al. Immunologic effect of zinc supplements and in HIV-infected children receiving highly active antiretroviral therapy: a randomized, double-blind, placebo-controlled trial. J Acquir Immune Defic Syndr 2014; 66(4): 386-92. [http://dx.doi.org/10.1097/QAI.0000000000000191] [PMID: 24797676]

[18] Asdamanogolo N, Phanachet P, Sungkansaparp S. Low plasma zinc levels and immunological responses to zinc supplementation in HIV-infected patients with immunological discordance after antiretroviral therapy. Jpn J Infect Dis 2013; 66(6): 469-74. [http://dx.doi.org/10.1088/jjid/06/04/036] [PMID: 24270132]

[19] Rahifudin MZ, Pradigdo SF. Pengaruh suplementasi seng terhadap CD4 pengidap human immunodeficiency virus. MGMI 2013; 5(1): 31-9. Available from: http://ejournal.litbang.kemkes.go.id/index.php/mgmi/article/view/3717

[20] Kaiser JD, Campa AM, Ondercin JP, Leoung GS, Pless RF, Baum MK. Micronutrient supplementation increases CD4 count in HIV-infected individuals on highly active antiretroviral therapy: a prospective, double-blinded, placebo-controlled trial. J Acquir Immune Defic Syndr 2006; 42(5): 523-8. [http://dx.doi.org/10.1097/01.qai.000025029.25083.42] [PMID: 16868496]

[21] Fawzi WW, Villamor E, Msamanga GI, et al. Trial of zinc supplements in relation to pregnancy outcomes, hematologic indicators, and T cell counts among HIV-1-infected women in Tanzania. Am J Clin Nutr 2005; 81(1): 161-7. [http://dx.doi.org/10.1093/ajcn/81.1.161] [PMID: 15640476]

[22] Green JA, Lewin SR, Wightman F, Lee M, Ravindran TS, Paton NI. A randomized controlled trial of oral zinc on the immune response to tuberculosis in HIV-infected patients. Int J Tuberc Lung Dis 2005; 9(12): 1378-84. [PMID: 16466061]

[23] Jiainthon S, Pepin J, Suttent R, et al. A randomized trial of the impact of multiple micronutrient supplementation on mortality among HIV-infected individuals living in Bangkok. AIDS 2003; 17(17): 2461-9. [http://dx.doi.org/10.1097/00002030-200311210-00008] [PMID: 14600517]

[24] Mocchegiani E, Vecchia S, Ancarani F, Scalfi G, Fabris N. Benefit of oral zinc supplementation as an adjunct to zidovudine (AZT) therapy against opportunistic infections in aids. Int J Immunopharmacol 1995; 17(9): 219-27. [http://dx.doi.org/10.1016/0192-0561(95)00060-F] [PMID: 8582783]

[25] Zeng L, Zhang L. Efficacy and safety of zinc supplementation for adults, children and pregnant women with HIV infection: systematic review. Trop Med Int Health 2011; 16(12): 1474-82. [http://dx.doi.org/10.1111/j.1365-3156.2011.02871.x] [PMID: 21895892]

[26] Kayode I, Anaba U. Effect of Vitamin D, selenium, or zinc supplementation in HIV: A systematic review. AIDS Rev 2020; 22: 1-10. [http://dx.doi.org/10.24875/AIDSRev.20000126]

[27] Jiang S, He J, Zhao X, et al. The effect of multiple micronutrient supplementation on mortality and morbidity of HIV-infected adults: A meta-analysis of randomized controlled trials. AIDS Rev 2020; 22: 1-10. [http://dx.doi.org/10.3177/jmv.58.105] [PMID: 22790568]

[28] Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Syst Rev 2017; 6(1): 245. [http://dx.doi.org/10.1186/s13643-017-0644-y] [PMID: 29208034]

[29] Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011; 343(oct18 2): d5928. [http://dx.doi.org/10.1136/bmj.d5928] [PMID: 22008217]

[30] WHO. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach 2010. Available from: https://apps.who.int/iris/bitstream/handle/10665/44379/9789241599764_eng.pdf?sequence=1

[31] Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. Nutrients 2020; 12(1): 236. [http://dx.doi.org/10.3390/nu12010236] [PMID: 31963293]

[32] Hujanen ES, Seppä S, Virtanen K. Polymorphonuclear leukocyte chemotaxis induced by zinc, copper and nickel in vitro. Biochim Biophys Acta, Gen Subj 1995; 1245(2): 145-52. [http://dx.doi.org/10.1016/0304-4165(95)00082-M] [PMID: 7492570]

[33] King LE, Frenzel JW, Mann JH, Fraker PJ. Chronic zinc deficiency in mice disrupted T cell lymphopoiesis and erythropoiesis while B cell lymphopoiesis and myelopoiesis were maintained. J Am Coll Nutr 2005; 24(6): 494-502. [http://dx.doi.org/10.1080/07315724.2005.10719495] [PMID: 16737496]

[34] Hönscheid A, Dubben S, Rink L, Haase H. Zinc differentially regulates mitogen-activated protein kinases in human T cells. J Nutr Biochem 2012; 23(1): 18-26. [http://dx.doi.org/10.1016/j.jnutbio.2010.10.007] [PMID: 21333516]

© 2022 Sindughosa et al.
This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International Public License (CC-BY 4.0), a copy of which is available at: https://creativecommons.org/licenses/by/4.0/legalcode. This license permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.