REVIEW PAPER

Effectiveness of nutritional intervention on immunity of people living with HIV/AIDS: a systematic review

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Abstract

An enormous progress has been made in the modality of treatment in human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) patients. In order to develop cure and enhance immune levels of people living with HIV/AIDS (PLHIV), major researches are being conducted across the globe. Nutritional intervention studies have been also conducted widely over a period of time to improve immune status of people living with HIV/AIDS, but concrete evidences in this regard are still lacking.

The objective of the study was to assess the effectiveness of selected nutritional interventions (zinc) on immunity of people living with HIV/AIDS. Search methods and selection criteria included randomized controlled trials investigating nutritional interventions, particularly with zinc. The effect of zinc on immune status of PLHIV was assessed. An extensive search from online databases, such as ProQuest, PubMed, Cochrane, and Science Direct was conducted from April 28, 2022 to May 28, 2022. Three reviewers independently screened and selected studies for inclusion. Cumulative sample size was 1,329 studies. After screening with PEDro scale and PRISMA reporting, five papers were considered to derive a consensus on the effect of zinc on immune status of PLHIV. As included studies were diverse in nature, meta-analysis was not possible to perform. Four studies revealed that zinc supplementation was not effective in enhancing immune system of PLHIV, whereas one study showed that zinc supplementation was effective in boosting immune level of PLHIV.

In conclusion, zinc supplementation is beneficial and safe among people living with HIV/AIDS as it boosts immunity, but further investigation is needed to generalize the findings.

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Key words: HIV, AIDS, PLHIV, zinc, immunity, CD4+ cell count.

Introduction

An enormous progress has been made in the modality of treatment in human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) patients. Initially, in 1980s, when the HIV global pandemic had emerged, there were no drugs to control it. Nowadays, life savings drugs to manage this disease are available [1]. A step further is required to transform HIV/AIDS from non-curable to

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completely curable or preventable disease by means of competent health interventions. In this regard, major attempts and researches are being conducted across the globe.

Nutritional interventions are also experimented widely over a period of time to improve immune status of people living with HIV/AIDS, but a concrete evidences in this regard are still lacking [2]. Nutritional factors play an important role in enhancing immunity, and their deficiency, particularly zinc, contribute to compromised immunity in people living with HIV/AIDS, as zinc, a trace element, is an immune booster. The most effective way to manage HIV/AIDS is by complementing anti-retroviral therapy with zinc. In this regard, to investigate the effectiveness of zinc, this current study was conducted. The objective of the study was to assess the effectiveness of selected nutritional interventions using zinc on immunity of people living with HIV/AIDS.

Material and methods

PICO framework was employed in the study, and is presented in Table 1.

A literature search was conducted from April 28, 2022 to May 28, 2022, and PEDro scale was applied to determine the quality of studies.

Criteria for studies' selection

Type of studies

This review considered any randomized control trial (RCT) that evaluate the effectiveness of nutritional intervention, particularly with zinc, on immunity of people living with HIV/AIDS.

Participants

The current research considered studies on people living with HIV/AIDS, who received any nutritional intervention in their therapy.

Types of interventions

Studies with the following interventions were deemed: "nutrients", "micro-nutrients", "trace elements", "minerals", "zinc", "nutritional support", "nutrition therapy", "diet therapy", "nutritional counselling".

Outcomes' measures: measure and time

Outcomes constituted the following aspects: 1) primary outcome: immune status; 2) secondary outcomes: viral load, serum zinc level, morbidity, CD4+ cell count, mortality, and opportunistic infections.

Search methods for identification of studies

An extensive search was carried out in online databases, including PubMed, Central, Science Direct, ProQuest, and Cochrane Library, with Cochrane database of systematic reviews and Cochrane central register of controlled trials (central). Various search strategies were adapted and included key words and mesh terms related to PICO (population, intervention, comparison, and outcome), such as "humans", "viruses", "HIV", "retroviridae", "HIV infections", "sexually transmitted diseases", "communicable diseases", "acquired immunodeficiency syndrome", "sarcoma Kaposi", "muscular atrophy", "HIV wasting syndrome", "nutrients", "micronutrients", "trace elements", "minerals", "zinc", "nutritional support", "nutrition therapy", "diet therapy", "nutritional status", "nutritional sciences", "immunity", "immune system", "antigens", "HIV antibodies", "CD4-positive T-lymphocytes", "viral load", "adaptive immunity", "immunity", "humoral".

All studies obtained through this search were subjected to quality check by using PEDro scale [3] to identify potential studies. PEDro scale included 11 items (Yes/No), and a score on PEDro scale < 4 was deemed weak, 5-6 was fair, 6-8 good, and 8-10 was considered optimal. Out of 213 studies, only 5 manuscripts were taken for recommendation as per inclusion criteria. Figure 1 presents PRISMA flow diagram with the details of the search [4].

Method of data collection and analysis

Selection of studies

Titles and abstracts of the selected studies were reviewed by the authors. The relevance to the topic was determined, and all the related articles were subjected to full-text review. On the review of full-text, the authors decided whether to include or not a study based on inclusion and exclusion criteria.

Inclusion criteria: All randomized controlled trials investigating nutritional intervention (zinc) for improving the immunity of people living with HIV/AIDS.

Exclusion criteria: 1. Pre-experimental studies on nutritional interventions for improving immunity of people living with HIV/AIDS. 2. Case reports on nutritional interventions for improving immunity of people living with HIV/

Table 1. PICO description

Population	Intervention	Comparison	Outcomes
People living with HIV/AIDS	Nutritional intervention	Standard care, usual care, routine care, placebo	Primary: Immunity Secondary: Viral load, CD4+ cell count, serum zinc level, mortality, morbidity, nutritional status

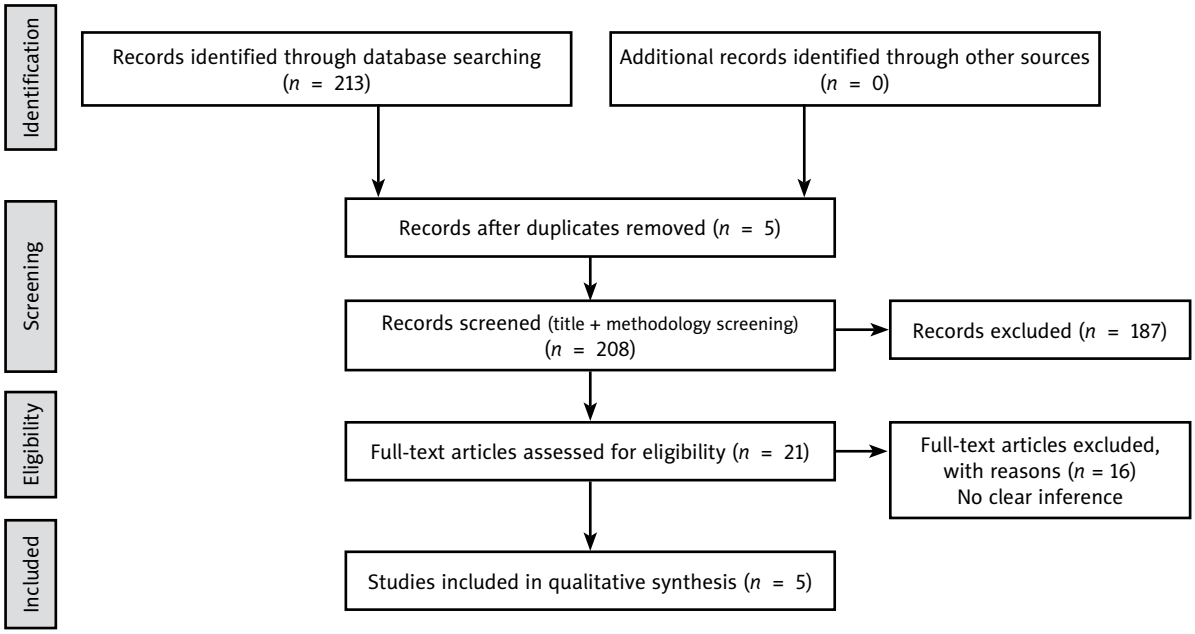

Figure 1. PRISMA flow diagram [4]

AIDS. 3. Other non-experimental or qualitative studies on nutritional interventions for improving immunity of people living with HIV/AIDS.

Studies included in this systematic review are shown in Table 2 [5-9].

Results

The review study showed that out of the 5 studies included, four revealed that zinc supplementation was not effective in enhancing immune system of PLHIV, whereas one study demonstrated the effectiveness of zinc supplementation in boosting immune level of PLHIV.

Discussion

In communities with high incidence and prevalence of HIV/AIDS, the mortality and morbidity rates are reported as high [10]. Antiretroviral therapy (ART) is found effective in decreasing the mortality rate among HIV-infected individuals [11]. In combination with ART, a complementary nutrient therapy, such as administration of micro- and macro-nutrients to avoid muscle wasting and strengthen immune system, can significantly contribute to elevate the effectiveness of ART [12]. In addition, zinc supplementation, in minimal dose for a longer period of time, may improve the immune status of patients with HIV/AIDS [13].

Zinc, despite being a trace element, plays a central role in immune system, and zinc-deficient person has an increased susceptibility to pathogens and infections. The immune function of zinc starts with skin barrier, resulting in activation of T lymphocytes, and it is essential for the development and functioning of cells mediating non-specific immunity, such as neutrophils. This review explored the biology of zinc in relation to immune system, and provided basis for drawing a consensus on credibility of immune system in zinc deficiency or zinc supplementation [14].

Our review identified various RCTs, contributing to the evidence supporting the effectiveness of zinc in enhancing HIV-positive patients' immunity, but only RCTs were included in this study to maintain homogeneity. Few RCTs showed no conclusive evidence on the effectiveness of zinc supplementation in enhancing immunity [6, 15, 16]. Hence, the effectiveness of zinc in relation to minimum dosage and maximum duration needs to be investigated. Given the features of zinc, it is indispensable to explore its vast potential, as it is cost-effective supplement, with minimum side effects [17].

Conclusions

Zinc appears to exhibit a promising property in complementing and strengthening ART among HIV/AIDS patients. In order to generalize the finding and further explore its potential, zinc needs to be rigorously experimented over a large sample size.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None

Table 2. Studies included in the review (n = 5)

No.	Authors [Ref.]	Title	Journal's name, year of publication	Sample size, setting	Interventions		Outcomes		Results
					Experimental group	Control group	Primary	Secondary	
1	Freiberg *et al.* [5]	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 Network Open, 2020	n = 254, St. Petersburg, Russia	Pharmacy-grade zinc gluconate supplementation (15 mg for men and 12 mg for women, taken daily orally for 18 months)	Placebo	The trial's primary outcome was a change in VACS index score	1. CVD risk 2. HIV disease progression 3. Biomarker levels of inflammation	Zinc supplementation did not reduce mortality risk, nor CD4+ cell counts, cardiovascular disease risk, and levels of inflammation or microbial translocation in people living with HIV/AIDS with heavy alcohol use
2	Dirajlal-Fargo *et al.* [6]	Zinc supplementation and inflammation in treated HIV	Journal of Acquired Immune Deficiency Syndromes, 2019	n = 52, Rainbow Babies and Children Hospital, USA	Zinc capsules 45 mg low-dose or 90 mg high-dose daily for 16 weeks	Placebo	The novel findings that zinc can affect biological marker in PLHIV and modulate clinical markers in comorbidities	Zinc was effective in increasing circulating zinc levels	Zinc was effective in increasing immunity levels of PLHIV
3	Ndeezi *et al.* [7]	Effect of multiple micro-nutrient supplementation on survival of HIV-infected children in Uganda: a randomized, controlled trial	Journal of the International AIDS Society, 2010	n = 847, Pediatric HIV clinics of the national referral hospital, Mulago	14 micro-nutrients as the intervention arm (vitamins A, B_1, B_2, niacin, B_6, B_{12}, C, D, E, folate, zinc, copper, iodine, and selenium)	The standard recommended dietary allowance of six multivitamins (vitamins A, D_2, B_1, B_2, C, and niacin)	Twice the recommended dietary allowance of 14 micro-nutrients compared	A standard recommended dietary allowance of six micro-nutrients	Multivitamins and micro-nutrients six months supplementation was well-tolerated, but it did not significantly alter mortality, growth, or CD4+ counts. Future intervention studies should carefully consider supplements' composition and dosing
4	Silva *et al.* [8]	Role and effects of zinc supplementation in HIV-infected patients with immune virological discordance: a randomized, double blind, case control study	PLoS One, 2021	n = 80, University of Chile School of Medicine	Patients with IVD were randomized to receive zinc (15 mg daily)	Placebo	Within the group of immune recovery of patients with hypozincemia, those with normozinchemia were analyzed and compared; no statistical difference was observed	–	Patients with IVD had plasma zinc levels similar to those, who achieved adequate immune recovery. Zinc supplementation in IVD patients showed a statistically non-significant difference in CD4+ levels in cases and controls
5	Bobat *et al.* [9]	Safety and efficacy of zinc supplementation for children with HIV-1 infection in South Africa: a randomized double blind, placebo, controlled trial	The Lancet, 2005	n = 96, Grey's Hospital, Pietermaritzburg, South Africa	10 mg of elemental zinc in PLHIV	Placebo	Plasma HIV-1 viral load	–	Zinc supplementation of HIV-1-infected children did not result in an increase of viral load in plasma HIV-1, and could reduce morbidity caused by diarrhea

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