Clinical Nutrition ESPEN 34 (2019) 1–7

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Review

Selenium supplementation in HIV-infected individuals: A systematic review of randomized controlled trials

Basilua Andre Muzembo*, Nlandu Roger Ngatu, Khatiwada Januka, Hsiao-Ling Huang, Choomplang Nattadech, Tomoko Suzuki, Koji Wada, Shunya Ikeda

Department of Public Health, School of Medicine, International University of Health and Welfare, Narita, Japan

ARTICLE INFO

Article history:
Received 13 March 2019
Accepted 6 September 2019

Keywords:
Selenium
Selenomethionine
Selenium deficiency
Selenium supplementation
HIV
AIDS

SUMMARY

Background & aim: HIV infection has been linked to selenium deficiency which, in turn, is thought to be associated with a high risk of tuberculosis and mortality in HIV-infected patients. Furthermore, several trials have reported the beneficial effects of selenium supplementation in patients with HIV. However, the evidence remains inconclusive. Our study aimed to investigate whether daily selenium supplementation in patients infected with HIV delays the progression of HIV infection.

Methods: A systematic review was performed using EMBASE and Medline databases from January 2000 to June 2018. We included randomized clinical trials in adults comparing selenium with placebo and reporting outcomes including its effect on HIV viral load and cluster of differentiation 4 cell count (CD4).

Results: Six out of the 507 retrieved articles that met the inclusion criteria were used in this review. Reviewed studies show that daily supplementation with 200 μg selenium may improve the rate of cluster of differentiation 4 (CD4) count. The length of selenium supplementation and follow-up varied from 9 to 24 months. Supplements were well tolerated in all reviewed studies. Whether daily selenium supplementation in HIV-infected persons suppresses HIV-infection requires further investigation as existing data are heterogeneous.

Conclusions: We found some clinical evidence that selenium supplementation can delay CD4 decline in HIV-infected patients, thus prolonging the onset of AIDS. However, we did not find quantifiable evidence that selenium supplementation suppresses or reduces HIV viral load.

1. Introduction

Despite significant advances in HIV-antiretroviral therapy, the HIV epidemic remains a significant health problem, and no definitive cure is in sight [1]. In 2017, an estimated 36.9 (31.1–43.9) million people were living with HIV worldwide [2]. However, only 47% of those living with HIV were virally suppressed as of July 2017 [3]. People living with HIV (PLWH) have an elevated risk of malnutrition [4]. In addition, micronutrient deficiencies, including selenium, are known to be prevalent during HIV-infection with significant effects on the immune system [5] and antioxidant defense [6]. Micronutrient deficiencies weaken immunity, thus can promote the progression of HIV-infection to AIDS. HIV-infection, in turn, aggravates micronutrient deficiencies, leading to a vicious circle.

Selenium (Se) is required for the biosynthesis of selenoenzymes, such as glutathione peroxidase, as it is incorporated into those proteins in the form of selenocysteine (Sec). Selenoenzymes protect against oxidative stress and activate thyroid hormones. Nonetheless, selenium is toxic if ingested in excessive amounts [7]. It is a micronutrient having potent antioxidant and anti-inflammatory functions mediated through selenoproteins [8]. Although selenium intake may benefit individuals with low selenium status,

Abbreviations: AIDS, acquired immune deficiency syndrome; ART, anti-retroviral therapy; CD4, cluster of differentiation 4 cell count; EMBASE, excerpta medica database; HAART, highly active anti-retroviral therapy; HIV, human immunodeficiency virus infection; PLWH, people living with HIV; PRISMA, preferred reporting Items for systematic reviews and meta-analyses; RCT, randomized controlled trials; Se, selenium; Sec, selenocysteine; US, United States.

* Corresponding author. Department of Public Health, School of Medicine, International University of Health and Welfare, 4-3 Kozunomori, Narita City, Chiba, 286-8686, Japan.

E-mail addresses: andersonbasilua@yahoo.fr, muzembo_andre@iuhw.ac.jp (B.A. Muzembo).

https://doi.org/10.1016/j.clnesp.2019.09.005

many of its biological and clinical benefits are relatively unknown to some clinicians [9]. Selenium supplementation is beneficial to PLWH [10]. The rationale for using selenium supplementation in HIV-infected persons stems from the hypothesis that selenium is a key micronutrient to maintain a responsive immune system [10] along with its potential to prevent HIV replication [11]. Furthermore, low selenium status is thought to be linked to a high risk of tuberculosis [12] and mortality [13,14] in HIV/AIDS patients.

However, selenium is not yet widely recommended in routine care in individuals infected with HIV. Some of the reluctance among clinicians to recommend selenium supplements is a result of a lack of clinical evidence and data, and our limited understanding about selenium supplementation in HIV-infected patients. Concerns have also been raised about high selenium status in HIV-1 infected adults being associated with clinical failure [5] and risk of increased HIV infectivity in women [15]. Randomized controlled trials (RCT) that have assessed the effects of selenium supplementation in PLWH have yielded heterogeneous results [16,17]. In 2007, daily selenium supplementation of 200 μg was reported to suppress HIV in American adults [11]. However, in 2015, findings from a Rwandan study using the same dose (200 μg) of selenium in HIV-infected adults failed to support the hypothesis that selenium can suppress HIV [18]. However, the authors recognized that selenium can improve the rate of cluster of differentiation 4 (CD4) count [18].

Using evidence from RCTs, we carried out this systematic review in an effort to find an answer to the following question: Does daily selenium supplementation in HIV-infected persons delay HIV-infection progression?

2. Methods

2.1. Study design and literature search

A systematic review was undertaken in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [19]. We conducted a systematic review of clinical trials in HIV-infected adults, with or without antiretroviral therapy, randomized to receive selenium supplementation or placebo. We conducted our literature search in the Excerpta Medica Database (EMBASE) and Medline (Between January 2000 and June 2018), using the following search terms: ('Human immunodeficiency virus' OR 'HIV' OR 'Acquired Immunodeficiency Syndrome' OR 'AIDS') AND ('selenium' or 'selenomethionine' or 'selenite') AND ('supplementation' or 'supplement'). Furthermore, the reference list of the selected studies and websites of major nutrition and AIDS journals (Between June and July 2018) were also checked for potentially eligible articles.

2.2. Inclusion and exclusion criteria

The study had to meet the following criteria to be included in this review: i) to be published as a RCT article comparing selenium supplementation to placebo; ii) to be performed in adults with a confirmed diagnosis of HIV. The outcomes of interest were the suppression of HIV and the reduction in CD4 decline. Accordingly, studies not reporting the aforementioned points and those clearly outside of our scope were excluded (examples included case-control and cohort studies). There were no publication language restrictions in the study selection process.

2.3. Data extraction

We separately assessed studies eligibility and extracted data using pre-conceived data extraction sheets. Once finished, any disagreements/discrepancies were resolved through discussion and further study evaluation. Extracted information included study characteristics (first author, setting, publication year, data collection year, sample size, and study design), patient characteristics (female percentage, mean or median age, and ART status), selenium form and dose, treatment duration and co-interventions, and potential side effects where applicable. The quality of the included studies was appraised using the Cochrane Risk of Bias Tool [20].

3. Results

3.1. Search

We retrieved 507 studies from our search (Fig. 1). Of these, 9 trials were potentially eligible [11,15,18,21–26]. Further screening eliminated three of these studies as they were deemed less relevant to our research question [15,25,26]. In the end, six RCTs evaluating the efficacy of selenium supplementation in adults infected with HIV were included in this review [11,18,21–24].

3.2. Study characteristics

Characteristics of the included RCTs are presented in Table 1 and Table 2. They were undertaken in four countries; two in the USA [11,23], two in Tanzania [21,24], and one each in Botswana [22] and Rwanda [18]. All studies were placebo-controlled, and they were published in English between 2002 and 2015. The number of participants ranged from 186 to 913, and their mean or median age ranged from 27 to 41 years. There was heterogeneity among the included studies regarding participants, their ART status (HIV-patient receiving and not receiving ART), CD4 count at baseline, and length of selenium supplementation. Two studies were performed in ART-naïve HIV-infected patients [18,22], two others in HIV-patients, most of which were receiving ART/HAART [11,23], and two studies included sole pregnant women [21,24]. In one study, participants received nevirapine (200 mg) to prevent transmission of HIV from mother to child [24] and of these pregnant women, thirty-one were receiving HAART at the end of the study [24]. All trials used the same selenium dosage of 200 μg/day. Four studies clearly stated that they used selenomethionine [11,18,21,24]. Nevertheless, two studies did not mention the selenium form used as a supplement [22,23]. Three studies used selenium as a single supplement [11,18,23], and two studies concomitantly used selenium with other micronutrient/multivitamins [21,24] or isoniazid prophylaxis [22] making it difficult for the authors to assess the effects of selenium alone.

Selenium status was mentioned only in two studies in which participants with selenium deficiency (<85 μg/L) at baseline were excluded [11,23]. However, in four studies, selenium status was unknown [18,21,22,24]. The total length of selenium supplementation and follow-up ranged from 9 to 24 months.

Regarding data analysis, the intention-to-treat (ITT) strategy was used in data analysis [11,18,21,22,24], with one exception that did not use the ITT method [23]. In addition, of the studies that used ITT, four studies used Cox proportional hazard ratio to model the effect of selenium supplementation on the endpoints; but one study used structural equation modeling to assess the impact of selenium increase on CD4 count and HIV viral load [11]. The quality of studies was acceptable, except one study that had high risk of attrition and reporting biases [11] (Table 3). Patient's compliance influences response to treatment. In primary studies, methods used to assess compliance included counseling [18,22], and counting the number of pills remaining in used bottles [11,21,22,24]. In one study, compliance was not clearly reported [23]. All studies had registered trial numbers. Of these studies, two had the same number and setting [21,24].

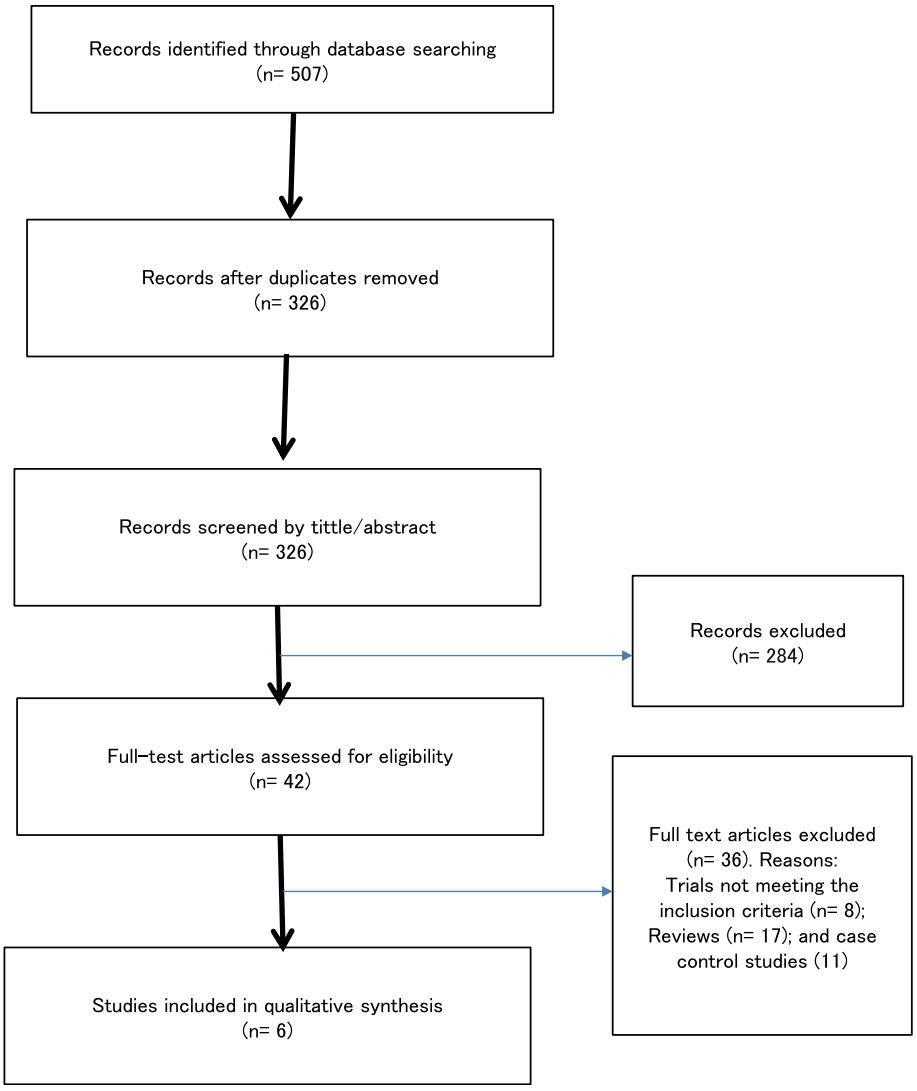

Fig. 1. Summary of evidence search and selection.

3.3. Efficacy of selenium supplementation

As shown in Table 4, four studies had concordant findings that selenium supplementation has the potential to delay CD4 decline in HIV-infected patients [11,18,22,23]. However, in one study, Baum et al. highlighted that a single supplement containing selenium and multivitamins, but not selenium alone, reduced the risk of CD4 decline in ART-naïve HIV-infected patients in Botswana [22]. But two studies by Kupka et al. carried out on pregnant women in Tanzania reported that selenium had no effect on CD4 cell count [21,24]. Kupka et al. noted that concomitant supplementation with high-dose multivitamins such as vitamin C and E might explain the lack of effect of selenium supplementation on maternal outcomes [21]. None of the studies with low-bias risk supported the hypothesis that selenium could suppress HIV. However, the study by Hurwitz et al. carried out on HIV-infected US adults suggested that a high selenium status can predict decreased HIV viral load [11]. Other beneficial effects of selenium supplementation included reduction of: i) the risk of child mortality after 6 weeks of age [21]; ii) diarrheal morbidity assessed through interview among pregnant women [24]; iii) hospitalizations of HIV-infected drug users mainly due to opportunistic infections and other HIV-related health conditions [23].

3.4. Adverse effects

Supplements were well tolerated by the participants in all reviewed studies. One fatality due to myocardial infarction occurred in HIV-infected individuals taking selenium supplement although the authors claimed that selenium supplementation was not the assumed cause of death. Two fatalities also occurred in patients supplemented with selenium and multivitamins but the cause of death was not imputed to supplementation [22]. One study reported no adverse effects related to selenium supplement [11]. Lastly, possible adverse effects were not described in three studies [21,23,24].

4. Discussion

In this review, the efficacy of selenium to delay the progression of HIV-infection was assessed. Six placebo-controlled RCTs were included. Overall, data from the reviewed RCTs suggest that supplementation with daily selenium (200 μg) among either ART-naïve HIV-infected patients or those receiving ART/HAART does not suppress HIV, but can delay the decrease in CD4 cell count and thus prolong the onset of AIDS.

However, like in other studies [16,17], we found that definitive conclusions cannot be drawn on the basis of these studies because

Table 1
Characteristics of randomized controlled studies of selenium supplementation in patients with HIV.

First author, year, setting	Sample size and participants	Multicenter	Study design	Selenium form and dose (μg/day)	Selenium combination	Length of supplement therapy and follow-up	Primary outcome
Kamwesiga [18], 2015, Rwanda	300 ART-naive HIV-infected patients (Treatment: 149; placebo: 151)	Yes	Prospective, randomized, double-blinded, placebo-controlled	Selenomethionine (200)	No	24 months	Change in CD4+ T-cell counts, start of ART, and progression to AIDS
Baum [22], 2013, Botswana	878 ART-naive HIV-infected patients (treatment:659; placebo: 219)	No	Randomized, double-blinded, placebo-controlled	Not reported (200)	Yes (Multivitamins alone and in combination with selenium for treatment group)	24 months	Impact on HIV-infection, and progression to AIDS
Kupka [24], 2009, Tanzania	913 ART-naive HIV-infected pregnant women[a] (Not reported)	Yes	Randomized, double-blinded, placebo-controlled	Selenomethionine (200)	Yes (ferrous sulfate and folic acid)	12–27 week of pregnancy to 6 months after delivery	Effect on hemoglobin and morbidity
Kupka [21], 2008, Tanzania	913 ART-naive HIV infected pregnant women (Treatment: 456; placebo: 459).	Yes	Randomized, double-blinded, placebo-controlled	Selenomethionine (200)	Yes (Additional supplements for treatment and placebo groups: Iron, folic acid, and multivitamin supplements)	12–27 week of pregnancy to 6 months after delivery	Effect on CD4 cell counts and viral load, pregnancy outcomes, and birth weight
Hurwitz [11], 2007, USA	262 HIV infected patients receiving ART (Treatment: 141; placebo:121)	Yes	Randomized, double-blinded, placebo-controlled	L-selenomethionine (200)	No	9 months	Effect on serum selenium, HIV-1 viral load and CD4 cell counts
Burbano [23], 2002, USA	186 Injection drug users (treatment: 89; placebo: 97)	No	Randomized, double-blinded, placebo-controlled	Not reported (200)	No	12 months	Impact on hospitalizations rate and cost

Definition of abbreviations: CD4 = cluster of differentiation 4; ART = antiretroviral therapy.
[a] Some pregnant women received highly active antiretroviral therapy around the end of the trial. Only 497 pregnant women [treatment (n = 250) and placebo (n = 247)] had available data to assess the effect of selenium supplementation on hemoglobin concentration at 6 months postpartum.

Table 2
Characteristics of HIV patients.

First author, year	Mean or median age (year)	Female, %	Data collection period	Mean/median CD4 at baseline in intervention group (cells/uL)	Apparatus used to quantify CD4	Apparatus used to quantify HIV viral load
Kamwesiga [18], 2015	Treated: 33.0; placebo: 35.0[a]	Treated: 70.9; placebo: 63.8	2012 to 2014	552[a]	Not reported	Not reported
Baum [22], 2013	Treated: 31–32; placebo: 33	Not reported	2004 to 2009	423–428	Cytocentrifuge smears and Coulter hematology analyzer	Roche Amplicor assay
Kupka [24], 2009	Treated and placebo: 27.7	100	2003/2005 to 2006	383	FAC-Scount system	Roche Amplicor HIV-1 monitor test, version 1.5 assay
Kupka [21], 2008	Treated: 27.4; placebo: 27.6	100	2003/2005 to 2006	375	FAC-Scount system	Roche Amplicor HIV-1 monitor test, version 1.5 assay
Hurwitz [11], 2007	Treated: 40.5; placebo: 40.6	Treated: 33.8; placebo: 31.7	2001 to 2005	417	Flow cytometry	Roche Amplicor HIV-1 monitor test, version 1.5 assay
Burbano [23], 2002	Treated: 41; placebo: 40	Treated: 44; placebo: 48	1998–2000	427	Flow cytometry	Amplicor HIV-1 monitor test

[a] Median.

they are heterogeneous, with only one study suggesting that selenium can reduce HIV viral load [11], and three studies suggesting that selenium supplementation alone does not affect HIV viral load and CD4 cell counts [21,22,24]. This heterogeneity did not allow us to perform a meta-analysis. The reasons behind this heterogeneity are certainly multifactorial.

Variability in studied patients (physiological differences), clinical stage of HIV infection, ART status (receiving or not receiving ART), ART regimen, combination of selenium with different supplements, the endpoints of interest, and length of treatment contributed somehow to the heterogeneity and makes comparison between studies difficult. For example, two studies conducted in Tanzania among HIV-positive pregnant women not receiving ART at the beginning of the treatment showed that selenium supplementation could not delay the progression of HIV-infection [21] or morbidity excluding diarrhea [24]. Nonetheless, the population in these studies differed substantially from two other studies carried out in the USA among HIV-infected patients receiving ART/HAART, reporting that selenium supplementation can delay the progression of HIV-infection [11] or reduce hospitalization [23]. These

Table 3
Assessment of risk of bias on the included studies using Cochrane criteria.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kamwesiga [18], 2015	Low	Low	Low	Low	Low	Low	Unclear
Baum [22], 2013	Low	Low	Low	Low	Low	Low	Unclear
Kupka [24], 2009	Low	Low	Low	Low	Unclear	Unclear	Unclear
Kupka [21], 2008	Low	Low	Low	Low	Unclear	Unclear	Unclear
Hurwitz [11], 2007	Low	Low	Low	Low	High	High	High
Burbano [23], 2002	Unclear	Low	Low	Unclear	Unclear	Unclear	Unclear

Table 4
Effects of selenium supplementation on HIV-infected patients in each study.

	First author, year					
	Kamwesiga [18], 2015	Baum [22], 2013	Kupka [24], 2009	Kupka [21], 2008	Hurwitz [11], 2007	Burbano [23], 2002
Reduction in CD4 decline	Yes	Yes[a]		No	Yes	Yes
Viral suppression	No	No	–	No	Yes	No
Reduction of child mortality after 6 weeks of birth	–	–	–	Yes	–	–
Overall child mortality	–	–	–	No		
Reduction of hospitalization	–	–	–	–	–	Yes
Reduced diarrheal morbidity	–	–	Yes	–	–	–
Improved hemoglobin	–	–	No	–	–	–

[a] This study used multivitamins combined with selenium as a single supplement.

mixed findings suggest that selenium supplementation may benefit specific HIV-infected patients but it may not be beneficial for other HIV-infected patients.

Importantly, it is not known how selenium status at baseline has influenced the endpoints in the primary studies because in most reviewed studies selenium status, which is germane to understanding changes in the expression of seleno-enzymes, was unknown [18,21,22,24]. Even though research has demonstrated that selenium supplementation has antiviral effects [11], mixed evidence from the reviewed studies serves as a crucial reminder that selenium supplementation should not be systematically undertaken in HIV-infected patients because of the U-shaped link between selenium intake and health [7]. It is imperative for clinicians to adopt a cautious approach before supplementing selenium in chronic illnesses such as HIV infection [27]. In HIV-infected patients, an assessment of selenium status should be recommended before supplementing selenium, especially when it is performed in combination with different synthetic anti-oxidants because supplementation with synthetic antioxidants such as beta-carotene, vitamin A and vitamin E may increase the risk of death and a combination of selenium with synthetic antioxidants does not have any beneficial effect [28]. The heterogeneity related to physiological differences found in this review provided some insight into our understanding of who should be supplemented with selenium when infected by HIV. For example, the studies by Kupka et al. that have looked at selenium supplementation in Tanzanian pregnant women could not detect any beneficial effect of selenium on maternal outcomes [21,24].

Selenium status correlates with dietary selenium supply and shows wide variance worldwide with some countries having a lower intake (Eastern Europe), a higher intake (Such as Canada, Japan, Venezuela, and the USA), and both higher and lower intakes (China) [7,8]. Relatively few reports have estimated dietary selenium intake in Africa although one study found that 28% are selenium-deficient [29]. Selenium supplementation is likely to be beneficial in individuals with inadequate intake and low selenium status [7]. For these reasons, large effects of selenium supplementation in theory would be seen in HIV-infected patients living in Africa and Eastern Europe. However, in those with relatively high selenium status, selenium supplementation may raise concerns because it can promote or exacerbate other health issues such as type 2 diabetes through insulin resistance [7,30]. Although it seems unlikely that selenosis will occur in HIV-infected patients as HIV reduces selenium levels, the possibility of health risk from high intake of selenium would be greater in countries such as the US. It is also important to note that in the studies carried out in the US [11,23], even though patients who were considered to have selenium deficiency were excluded, the two studies reported encouraging results. But the results of these two studies cannot be generalized to HIV-infected patients who do not receive ART because most participants in these two studies were receiving ART/HAART.

In addition, the quality of reporting in the reviewed studies should also be taken into account when interpreting the results presented in this review. The risk of bias varied across studies. Notably, the studies performed in ART-naïve patients by Kamwesiga et al. [18] in Rwanda (selenium alone) and that by Baum et al. [22] in Botswana (selenium combined with multivitamins) supporting no beneficial effect of selenium on HIV viral load were likely to have a low risk of bias. However, the two studies carried out in the USA [11,23] presenting promising outcomes (that selenium can reduce HIV viral load and hospitalization) have been criticized as being vulnerable to bias [27,31]. Most of the included studies used

200 μg Se/day in the form of selenomethionine. One obvious interpretation for the use of selenomethionine is probably its absorption and bioavailability. Dietary selenium has various forms, organic (selenomethionine) and inorganic (selenite/selenate) forms, the form most commonly ingested being selenomethionine, which is transformed into Sec [8]. The degree of absorption of selenomethionine and its retention in the body are greater than selenite or selenate [32]. Selenite, selenate, and selenium-enriched yeast (a mixture of several selenium forms) have been used for selenium supplementation [33]. Therefore, it is worth testing these selenium forms in future trials. Unfortunately, we were unsuccessful in our attempts to find out on which base the dose of 200 μg Se/day was calculated. The choice of using 200 μg Se/day was probably influenced by the first trial on selenium supplementation in HIV-infected conducted in the US [11] along with previously published reports such as the Nutritional Prevention of Cancer (NPC) Trial where 200 μg/day of selenium was used [34].

The proposed mechanism by which selenium supplementation might benefit HIV-infected patients varies according to selenium's ability to protect against oxidative stress through glutathione peroxidase [35] and modulate cell-mediated and humoral immunity, all of which are important to hamper HIV replication and to fight against infection [6]. Notably, adequate selenium status upregulates the production of interleukin (IL) 2 and helps naïve CD4-positive T cells to proliferate and differentiate towards T helper (Th) 1 cells, thus supporting the cellular-mediated immune response to HIV [36]. In addition, adequate selenium status also has the potential to down-regulate the abnormally elevated concentrations of IL-8 and tumor necrosis factor-alpha (TNF-alpha) which had been associated with increased HIV replication [36]. On the other hand, low selenium status boosts immune cells by skewing the differentiation of naïve CD4-positive T cells into Th2 effectors, which can increase the progression of HIV-infection [6].

Electronic databases were searched up until 6 August 2018 for recent systematic reviews reporting on selenium supplementation in HIV-infected patients. We identified some comprehensive reviews reporting on this topic [16,17,37]. Their results indicate, to a certain degree, the same direction as our results. While our results are somewhat similar to these three reviews, there are some differences between these studies that deserve mentioning. Firstly, two reviews were not exclusively related to selenium [17,37] and secondly, one study included trials without control groups [16]. The inclusion of only placebo-controlled RCTs makes the results of this review more robust, amid the growing literature on selenium and HIV, which is dominated by non-randomized/observational studies that show little evidence and are vulnerable to confounding bias.

5. Conclusion

We did not find any quantifiable evidence that selenium supplementation suppresses HIV but the reviewed studies show that selenium can delay the decline in CD4 in specific patients infected with HIV. However, we are unable to arrive at any definitive conclusions at this stage. The question about whether “daily selenium supplementation in HIV-infected persons delays HIV-infection progression to AIDS” still needs further investigation in adequately-performed and analyzed RCTs that assess the effect of selenium supplementation in adults living with HIV and receiving, or not receiving standardized ART/HAART.

Contributors

BAM and NRN were responsible for the design, data collection, and data synthesis. BAM wrote the first draft of the manuscript. NRN, KJ, HLH, CN, TS, KW and SI revised and edited the manuscript.

Funding

“This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.”

Declaration of interests

None to declare.

Acknowledgements

The authors would like to thank Mr. Matthew McLaughlin from the International University of Health and Welfare and Mrs. Mansongi Biyela Carine for their helpful suggestions through the preparation and composition of this manuscript.

References

[1] Bekker LG, Alleyne G, Baral S, Cepeda J, Daskalakis D, Dowdy D, et al. Advancing global health and strengthening the HIV response in the era of the sustainable development goals: the international AIDS society-lancet commission. Lancet 2018;392(10144):312–58.
[2] UNAIDS: Global HIV statistics 2017. Accessed August 20, 2018, at: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf.
[3] UNAIDS: UN Joint Programme on HIV/AIDS (UNAIDS), Global AIDS Update - 2018. Accessed August 30, 2018, at: http://www.unaids.org/en/20180718_GR2018.
[4] Ivers LC, Cullen KA, Freedberg KA, Block S, Coates J, Webb P. HIV/AIDS, undernutrition, and food insecurity. Clin Infect Dis 2009;49(7):1096–102.
[5] Shivakoti R, Gupte N, Yang WT, Mwelase N, Kanyama C, Tang AM, et al. Pre-antiretroviral therapy serum selenium concentrations predict WHO stages 3, 4 or death but not virologic failure post-antiretroviral therapy. Nutrients 2014;6(11):5061–78.
[6] Baum MK, Miguez-Burbano MJ, Campa A, Shor-Posner G. Selenium and interleukins in persons infected with human immunodeficiency virus type 1. J Infect Dis 2000;182(Suppl 1):S69–73.
[7] Rayman MP. Selenium and human health. Lancet 2012;379(9822):1256–68.
[8] Muzembo BA, Deguchi Y, Ngatu NR, Eitoku M, Hirota R, Suganuma N. Selenium and exposure to fibrogenic mineral dust: a mini-review. Environ Int 2015;77:16–24.
[9] Hatfield DL, Gladyshev VN. How selenium has altered our understanding of the genetic code. Mol Cell Biol 2002;22(11):3565–76.
[10] Campa A, Martinez S, Baum M. Selenium in HIV/AIDS. In: Hatfield Dolph L, Schweizer Ulrich, Tsuji Petra A, Gladyshev Vadim N, editors. Selenium, vol. 2016; 2016. p. 333–42.
[11] Hurwitz BE, Klaus JR, Llabre MM, Gonzalez A, Lawrence PJ, Maher KJ, et al. Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation: a randomized controlled trial. Arch Intern Med 2007;167(2):148–54.
[12] Muzembo BA. Serum selenium levels in tuberculosis patients: a systematic review and meta-analysis. 2018.
[13] Kupka R, Msamanga GI, Spiegelman D, Morris S, Mugusi F, Hunter DJ, et al. Selenium status is associated with accelerated HIV disease progression among HIV-1-infected pregnant women in Tanzania. J Nutr 2004;134(10):2556–60.
[14] Rayman MP. The importance of selenium to human health. Lancet 2000;356(9225):233–41.
[15] McClelland RS, Baeten JM, Overbaugh J, Richardson BA, Mandaliya K, Emery S, et al. Micronutrient supplementation increases genital tract shedding of HIV-1 in women: results of a randomized trial. J Acquir Immune Defic Syndr 2004;37(5):1657–63.
[16] Stone CA, Kawai K, Kupka R, Fawzi WW. Role of selenium in HIV infection. Nutr Rev 2010;68(11):671–81.
[17] Visser ME, Durao S, Sinclair D, Irlam JH, Siegfried N. Micronutrient supplementation in adults with HIV infection. Cochrane Database Syst Rev 2017;5:CD003650.
[18] Kamwesiga J, Mutabazi V, Kayumba J, Tayari JC, Uwimbabazi JC, Batanage G, et al. Effect of selenium supplementation on CD4+ T-cell recovery, viral suppression and morbidity of HIV-infected patients in Rwanda: a randomized controlled trial. AIDS 2015;29(9):1045–52.
[19] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151(4):264–9. W264.
[20] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[21] Kupka R, Mugusi F, Aboud S, Msamanga GI, Finkelstein JL, Spiegelman D, et al. Randomized, double-blind, placebo-controlled trial of selenium supplements among HIV-infected pregnant women in Tanzania: effects on maternal and child outcomes. Am J Clin Nutr 2008;87(6):1802–8.

[22] Baum MK, Campa A, Lai S, Sales Martinez S, Tsalaile L, Burns P, et al. Effect of micronutrient supplementation on disease progression in asymptomatic, antiretroviral-naive, HIV-infected adults in Botswana: a randomized clinical trial. JAMA 2013;310(20):2154–63.
[23] Burbano X, Miguez-Burbano MJ, McCollister K, Zhang G, Rodriguez A, Ruiz P, et al. Impact of a selenium chemoprevention clinical trial on hospital admissions of HIV-infected participants. HIV Clin Trials 2002;3(6):483–91.
[24] Kupka R, Mugusi F, Aboud S, Hertzmark E, Spiegelman D, Fawzi WW. Effect of selenium supplements on hemoglobin concentration and morbidity among HIV-1-infected Tanzanian women. Clin Infect Dis 2009;48(10):1475–8.
[25] Flax VL, Bentley ME, Combs Jr GF, Chasela CS, Kayira D, Tegha G, et al. Plasma and breast-milk selenium in HIV-infected Malawian mothers are positively associated with infant selenium status but are not associated with maternal supplementation: results of the Breastfeeding, Antiretrovirals, and Nutrition study. Am J Clin Nutr 2014;99(4):950–6.
[26] Durosinmi MA, Armistead H, Akinola NO, Onayemi O, Adediran IA, Olasode OA, et al. Selenium and aspirin in people living with HIV and AIDS in Nigeria. Niger Postgrad Med J 2008;15(4):215–8.
[27] Pitney CL, Royal M, Klebert M. Selenium supplementation in HIV-infected patients: is there any potential clinical benefit? J Assoc Nurses AIDS Care 2009;20(4):326–33.
[28] Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA 2007;297(8):842–57.
[29] Joy EJ, Ander EL, Young SD, Black CR, Watts MJ, Chilimba AD, et al. Dietary mineral supplies in Africa. Physiol Plant 2014;151(3):208–29.
[30] Rocourt CR, Cheng WH. Selenium supranutrition: are the potential benefits of chemoprevention outweighed by the promotion of diabetes and insulin resistance? Nutrients 2013;5(4):1349–65.
[31] Ross DA, Cousens S, Wedner SH, Sismanidis C. Does selenium supplementation slow progression of HIV? Potentially misleading presentation of the results of a trial. Arch Intern Med 2007;167(14):1555–6. author reply 1557.
[32] Fairweather-Tait SJ, Bao Y, Broadley MR, Collings R, Ford D, Hesketh JE, et al. Selenium in human health and disease. Antioxidants Redox Signal 2011;14(7):1337–83.
[33] Thomson CD, Robinson MF, Butler JA, Whanger PD. Long-term supplementation with selenate and selenomethionine: selenium and glutathione peroxidase (EC 1.11.1.9) in blood components of New Zealand women. Br J Nutr 1993;69(2):577–88.
[34] Clark LC, Combs Jr GF, Turnbull BW, Slate EH, Chalker DK, Chow J, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. J Am Med Assoc 1996;276(24):1957–63.
[35] Stephensen CB, Marquis GS, Douglas SD, Kruzich LA, Wilson CM. Glutathione, glutathione peroxidase, and selenium status in HIV-positive and HIV-negative adolescents and young adults. Am J Clin Nutr 2007;85(1):173–81.
[36] Steinbrenner H, Al-Quraishy S, Dkhil MA, Wunderlich F, Sies H. Dietary selenium in adjuvant therapy of viral and bacterial infections. Adv Nutr 2015;6(1):73–82.
[37] Alicia S, Adriana C, Marianna KB. Review of randomized controlled trials of nutritional supplementation in people living with HIV. Nutr Diet Suppl 2016;8:21–39.