Selenium deficiency and HIV infection

Stefano Di Bella, Elisabetta Grilli, Maria Adriana Cataldo, Nicola Petrosillo
National Institute for Infectious Diseases “L. Spallanzani”, Rome, Italy

Abstract

Selenium is a non-metallic chemical element of great importance to human health. Low selenium levels in humans are associated with several pathological conditions and are a common finding in HIV infected individuals. We conducted a review of the literature to assess if selenium deficiency or selenium supplementation could play a role in modifying the clinical course of HIV disease.

Several studies investigated the role of selenium in disease progression, morbidity and mortality in HIV infected individuals. Larger studies were conducted in countries with poor economic resources and limited access to HAART. According to the majority of published studies low selenium levels appear to have an association with mortality, and selenium supplementation appears to play a beneficial role on survival or on slowing disease progression among HIV infected individuals. The role of selenium supplementation on preventing hospital admission among HIV outpatients was also noticed. The literature suggests an association between selenium deficiency and development of HIV associated cardiomyopathy and furthermore, selenium supplementation appears to improve the cardiac function in HIV infected individuals with cardiomyopathy. However, there is conflicting evidence regarding the role selenium in modifying HIV viral load and immune status in HIV infection.

Introduction

Micronutrient supplementation has shown beneficial effects among the human immunodeficiency virus (HIV) infected population and there has been increasing interest in supplementation as a therapeutic strategy. Selenium is a non-metallic chemical element deriving from both vegetables and animal products, in particular seafood, liver and cereals. Since the late 1960’s, its role on humans’ health has been extensively investigated.

Selenium is a key component of several human selenoproteins and mostly involved in redox reactions. It is required for the activity of the enzyme glutathione peroxidase (GPX), a main intracellular antioxidant, that acts to prevent oxidation-induced cellular damage. Chronic exposure to high levels of selenium may be associated with several health problems in humans such as nail and hair loss, gastroenteritis and dermatitis but the most important health effects are related to the deficient state. The normal ranges of serum selenium plasma levels in adults are 1.1 to 2.5 μmol/L in blood and 0.75 to 1.35 μmol/L. The minimum daily intake of selenium is recommended at 30 μg. Selenium deficiency in humans is associated with an increased incidence of cancer, cardiomyopathy (including Keshan disease), a deforming osteoarthropathy (Kashin-Beck disease), male sub-fertility, liver dysfunction, mood disorders, skeletal muscle disorders, impaired thyroid hormone metabolism, impaired immune function, progression of HIV infection and mortality.

The first studies were published on the role of selenium in HIV-infected patients in 1989. The aim of this review is to summarise the evidence regarding the relationship between selenium and HIV infection.

Materials and Methods

We carried out a literature review of published studies that evaluated the relationship between serum/plasma selenium status or selenium supplementation and HIV disease in human subjects. The search was performed through the PubMed database and restricted to full articles published up to September 2009, irrespective of language. No attempt was made to obtain information about unpublished studies.

Index search terms included the Medical Subjects Heading selenium, HIV, AIDS, immunodeficiency, malnutrition, co-infection, opportunistic infections, AIDS progression, AIDS-related neoplasm, viral load, CD4, AIDS stage.

Studies were considered eligible if they presented data pertaining to the relationship between selenium and HIV disease. Reviews, editorials, case reports and literature regarding animal or in vitro studies were excluded.

We did not include results concerning the relationship between selenium and HIV genitourinary shedding.

Results

Our literature search identified 195 articles. Among these we found 33 studies that met our search criteria. In summary, we found 13 cross-sectional studies, 11 prospective observational studies and 9 clinical trials.

Selenium and sero-status of HIV

The possible relationship between serum selenium levels and the sero-status of HIV has been analysed in 12 studies. The majority of these reported a significant association between HIV infection and low serum selenium levels. However, three studies comparing HIV-positive to HIV-negative subjects did not find a significant relationship between HIV-infection and selenium deficiency. It is possible that these studies failed to demonstrate a significant association due to small sample sizes and the inclusion of severely malnourished subjects in both the HIV-positive and HIV-negative study groups.

Selenium and HIV disease stage/disease progression

An association between selenium levels and HIV disease stage (including CD4 cell counts, opportunistic infections, AIDS-related neoplasm and viral load) has been reported by seven authors.

Cirelli et al. measured serum selenium concentration in four groups of HIV-infected patients: symptom-free subjects, persistent generalized lymphadenopathy (PGL), AIDS related complex (ARC) and AIDS. Serum selenium concentrations were significantly higher in symptom-free HIV positive subjects as compared to the other three groups. Similarly, Constans et al. observed that serum levels of selenium were lower in patients with a count
### Table 1. Relevant studies on selenium and HIV infection published in the literature.

| Author/Year | Study population | Objectives and/or End Points | Results |
|-------------|------------------|------------------------------|---------|
| Grelli 1991**<sup>11</sup> | 67 HIV+ male pts Group 1: 23 pts symptom-free subjects Group 2: 7 pts with PGL Group 3: 7 with ARC Group 4: 30 AIDS patients Group 5: 15 HIV controls | To assess the Se status of HIV+ pts; the relationship between different stages of HIV disease and Se deficiency; to verify if Se supplementation improves immunological function. | Se was normal in Group 1 pts and lower in Groups 2-3-4 pts Group 4 showed a positive correlation between Se levels and Hb and ESR Positive increase of Se levels in pts receiving Se [80 µg/day] supplementation |
| Constans 1993<sup>11</sup> | 77 HIV+ Group 1: CD4 <50 Group 2: CD4 50-200 Group 3: CD4 200-400 Group 4: CD4 >400 20 HIV- controls | To investigate Se role on oxidative metabolism in HIV+ pts | Serum Se correlated with CD4 cell count (univariate) Serum Se correlated with p24 antigenemia (univariate) Death was correlated with serum Se (univariate) Occurrence of OI correlated with serum Se (univariate) Death correlated with serum Se (multivariate) OI correlated with serum Se (multivariate) |
| Constans 1995<sup>11</sup> | 95 HIV+ followed for 1 year - 34 died - 47 had an AIDS-defining OI | To investigate the role of selenium in predicting outcome among HIV+ pts | Se levels were low in Groups 1-2-3 Se was correlated with body mass index (BMI) |
| Look 1997<sup>17</sup> | 104 HIV+ (28 coinfected with HCV): - 33 CDC I pts - 34 CDC II pts - 37 CDC III pts (among these 21 pts with either acute OI and/or AIDS defining tumors) 72 healthy controls | To investigate antioxidant defence status and surrogate markers of HIV disease in HIV-infected patients | Se levels were lower in CDC II-III pts vs CDC I pts Se levels were lower in CDC II-III pts vs healthy controls Se levels were lower in CDC III pts vs CDC II pts Se levels were positively correlated with CD4 count CD4 was not independently correlated with Se (multivariate) Se levels of coinfected pts (HIV/HCV) were lower than HIV infected only pts Se levels were lower in CDC III pts with OI or AIDS defining tumors than in the remaining CDC III pts |
| Ndage 2007<sup>12</sup> | 112 severely malnourished Rwandan children: 52 HIV- (none on ART) 60 HIV- | To determine levels of CD4 cells and micronutrients in HIV- and HIV- severely a malnourished Rwandan children | One third in both groups (HIV- and HIV-) had low Se levels No significant difference in Se levels between HIV- and HIV- children Correlation between Se and regression of CD4 in HIV+ children (multivariate) Correlation between Se and regression of CD4 in HIV+ children (multivariate) |
| Burbano 2002<sup>13</sup> | 186 HIV+ - 89 Se supplemented group - 97 pbll supplemented group | To evaluate the impact of Se chemoprevention (200 µg/day) on hospitalizations in HIV+ individuals. | Pbll-group had higher CD4 decline than Se-receiving group Se group had lower admission rate than pbll group Se group had lower % of hospitalization than pbll group Cost for hospitalization was lower in Se group than in Pbll group Se is an independent factor for ↓ risk of hospitalization |
| McClelland RS 2004<sup>**8</sup> | 400 HIV+ ART-naive pregnant Kenyan women: - 200 multivitamin + Se (200 µg) supplemented pts - 200 placebo supplemented pts | To evaluate CD4, VL and cervical and vaginal shedding of HIV-1 infected cells and RNA in women treated or not treated with micronutrient supplementation for 6 weeks | Micronutrient group had ↑ CD4 vs pbll group Micronutrient group had ↑ CD8 vs pbll group No relationship between micronutrients and VL |
| Hurwitz 2007<sup>**9</sup> | 174 HIV- (9-month FU assessment): - Se group = 91 pts - Pbll group = 83 pts | To evaluate the effect of Se supplementation [200 µg/d for 9 months] on serum Se levels and the subsequent impact on HIV-1 viral load and CD4 count. | Se group had greater change in serum Se at the 9-months assessment. Se responders (50/91) had greater increases in serum Se concentration than pbll and nonresponders Se responders (50/91) had less viral load increase than pbll and nonresponders Se responders (50/91) had greater CD4 count increase than pbll and nonresponders |

Continued next page
| Author/Year | Study population | Objectives and/or End Points | Results |
|------------|------------------|-----------------------------|---------|
| Alavena 1995<sup>1</sup> | 80 HIV + at stage IV (CDC) | To evaluate relationship between trace elements, β2 microglobulin and HIV infection progression | Group 1 had lower Se levels than Group 2 pts. Se levels in all HIV pts of the study were lower than normal values of Se. |
| Beck 1990<sup>6</sup> | 59 HIV (male) | To compare serum concentrations of selected elements in HIV+ pts vs healthy controls | In HIV+ pts direct correlation between serum Zn and Se. No significant correlations between stage of the disease and Se. |
| Hoffman 1997<sup>6</sup> | 125 HIV + drug users | To evaluate nutritional status and immune parameters in HIV+ who abuse drugs | HIV+ women had lower Se than the HIV+ men. HIV+ women had higher proportion of Se deficiency than the HIV- men. Among pts with CD4 < 200, Se levels were lower in women vs men. |
| Campa 1999<sup>6</sup> | 24 HIV+ children observed for 5 yrs (12 died over the course of the study of HIV-related causes) | To determine the contribution of specific nutritional factors on disease progression and survival in HIV + children | Se deficiency was significantly and independently related to mortality. Survival time was shorter in selenium deficient children. Among the children who died, those with low Se died at younger age. |
| Delmas-Beauvieux 1996** | 45 HIV+ pts with CD4 < 400: - 18 placebo group, - 14 Se group (100 µg/d), - 13 β-carotene group, 26 healthy adults (control group) | To investigate (1 year) the effect of Se (100 µg/d) and β-carotene supplementation in HIV+ pts. | Plasma Se at baseline was lower in HIV+ than in controls. |
| Ogunro 2006<sup>1</sup> | 100 HIV+ (before beginning ART) | To investigate a relationship between plasma Se concentration and erythrocyte activity in HIV+ pts with the progression of the disease. | Plasma Se ↓ in HIV with CD4 < 200 vs controls. Plasma Se ↓ in HIV with CD4 200-499 vs controls. |
| Tohill 2007<sup>12</sup> | 369 HIV+ women | To assess nutritional biomarkers associated with several gynecological conditions in women with or at risk of HIV infection. | HIV+ women had ↓ Se values vs population median values. |
| Khalili 2008<sup>1</sup> | 100 healthy controls | Compare nutritional status of Iranian subject newly diagnosed with HIV infection with control healthy subjects. | Serum Se was significantly lower in HIV group vs control group. Serum Se in IVDU was significantly lower than in sexually infected individuals. Serum Se in HIV pts positively correlated with malnutrition levels. |
| Forrester 2009<sup>6</sup> | 300 US Hispanic adults (4 groups): - HIV+ drug users, - HIV+ drug users, - HIV+ who do not use drugs, - healthy persons who denied drug use | To examine the effects of HIV, HCV and drug use on micronutrients in HIV+ pts. | HIV infection was associated with ↓ Se. Low Se levels (<85 µg/L) were more prevalent in co-infected (HIV/HCV) pts. ART CD4 count, VL were not predictors of micronutrient status in HIV+ pts. No interaction effect between HIV and HCV for any micronutrient (including Se). |
| Stephens 2007<sup>10</sup> | 244 HIV+ adolescents, 121 HIV+ adolescents | To determine if HIV infection is associated with poor Se status and low antioxidant protection. | HIV status was a significant negative predictor of plasmatic Se. Mean Se concentrations were lower in women than in men. Plasma Se was not associated with VL. |
| Author/Year | Study population | Objectives and/or End Points | Results |
|------------|------------------|-----------------------------|---------|
| Henderson 1997 | 39 HIV+ with growth retardation | Evaluate Se, plasma protein and micronutrient levels in HIV | No significant differences between groups in the frequency of deficiency for any nutrient studied (Se included). |
| Malvy 1994 | 18 HIV+ children with or without growth retardation | To evaluate the relationship of plasma malondialdehyde, vitamin E and antioxidant micronutrients to HIV-1 seropositivity | Controls: Group A (Gr. A): 40 HIV+ hemophilic children (Gr. A) — 20 healthy boys (Gr. C) Group B: 10 HIV+ hemophilic children (Gr. B) 10 healthy boys (Gr. C) | No differences in Se levels between Groups A, B, and C |
| Look 1998 | Two groups: A (13 pts), B (11 pts): A. HIV+ treated from wk 1 to wk 24 — B. HIV+ treated from wk 12 to wk 24 | To evaluate effects of NAC [600 mg t.i.d] and Se on plasma GSH, erythrocyte GSH-Px activity, and lymphocyte subpopulations and HIV-1 levels | Increase in CD4 percentage at week 6 in Group A. Group B: Decrease in the absolute CD4/CD8 count after 6 weeks in Group A vs Group B. Decrease in the CD4% changes in VI-A after 6 weeks in Group B vs Group A. No changes in VI-A after NAC/Se treatment (both Group A and B) |
| Constans 1996 | 15 HIV+ supplemented with Se and 22 HIV+ non supplemented (controls) | To assess the effect of Se supplementation on CD4 cell counts | No effect of Se supplementation on CD4 cell counts in 15 HIV+ supplemented with Se and 22 HIV+ non supplemented (controls) |
| Jones 2006 | 181 HIV+ on HAART | To determine the prevalence of micronutrient deficiencies in HIV-1-infected patients receiving HAART and to assess the association of micronutrient deficiencies with HAART and CD4+ T-cell counts | No significant correlation between Se concentration and CD4+ T-cell counts. |
| Drain 2006 | 400 HIV+ ART-naive women | To evaluate the relationship between serum Se and CD4, VL, serum albumin and ACR | Serum Se was not significantly associated with CD4, VL, and ACR. |
| Baeten 2001 | 318 HIV+ Kenyan women | To assess the relationship between Se deficiency and vaginal or cervical shedding of HIV-1-infected cells in asymptomatic HIV-1-infected women. | No significant correlation between Se concentration and CD4+ T-cell counts. |
| Rousseau 2000 | 77% IVDU patients receive HAART and 19% did not. Among the 77% who received HAART in 1995, 77% had low Se levels. In 1998, 10% had low Se levels. | To assess micronutrient variations in HIV/AIDS patients treated with HAART | No significant correlation between Se concentration in 1995 and 1998 and the development of CD4+ T-cell counts. |
| Kelly 1999 | 135 HIV+ patients: A. micronutrient-treated group 66 micronutrient-treated group for 2 weeks in the AIDS diarrhea-wasting syndrome in Zambia | To evaluate the effect of Se supplementation on diarrhoea | No difference between micronutrient-treated and placebo-treated groups for diarrhoea-wasting syndrome in Zambia. |
| Shor-Posner 2002 | 8 HIV+ drug users (2 yrs observation) | To investigate the impact of Se status on the development of mycobacterial disease in HIV+ drug users | Se ≤ 13 µg/L was associated with 13x risk of mycobacterial disease vs Se > 13 µg/L. |
| Zasso 1988 | 10 AIDS patients with nonobstructive cardiomyopathy | To prospectively evaluate the effect of Se supplementation on cardiomyopathy | Se > 13 µg/L was associated with 13x difference in the risk of mycobacterial disease. |
| Twagirumukiza 2007 | 416 HIV+ Rwandan patients (71 affected by DCM P) | To assess the prevalence of DCM P in HIV and to investigate risk factors associated with its development | Low Se increases risk of mycobacterial diseases in HIV (multivariate analysis). |

** indicates a clinical trial.
of CD4 less than 400 cells/mm³. Another study reported that opportunistic infections occurred more frequently among patients with lower serum selenium concentration. In a cross-sectional study on 104 HIV-infected individuals Look et al. reported that mean serum selenium levels were significantly lower in patients at CDC HIV stage II and III as compared to healthy subjects and to HIV stage I patients.

In addition, three clinical trials reported a slower decline in CD4 or an increase in CD4 cell counts in patients receiving oral selenium supplementation and these are briefly described below. Burbano et al. conducted a randomized, double-blind, placebo-controlled trial on 186 HIV-infected individuals and showed that the placebo group had a more rapid decline in CD4 count than the selenium-supplemented group. A further randomized, double-blind, placebo-controlled supplementation trial (micronutrients + 200 μg/day of selenium) designed by McClelland et al., involving 400 pregnant HIV positive women in Kenya, showed that the selenium-supplemented group had higher CD4 levels than the placebo group.

Hurwitz et al. administered either supplementation with selenium (200 μg/day) or placebo to 174 HIV subjects for 9 months. At the end of the follow-up period, an higher increase in CD4 count was observed among selenium responders (individuals whose mean serum selenium concentration changed more than 3 standard deviations above the mean serum selenium concentration change of the placebo group) than that recorded in the placebo and selenium non-responder groups. Authors performed an analysis to examine if the effect on CD4 count was mediated by the viral load change. Interestingly, a model with several covariates (including HIV disease stage, antiretroviral treatment and adherence to it) confirmed that, in this study, selenium treated patients had a significant decrease in HIV viral load.

Seven studies did not demonstrate a significant relationship between selenium levels or supplementation and CD4 cell count or disease status. However, Rousseau et al. failed to find a relationship between selenium levels and CD4 cell count or disease status in a study which looked at patients treated with highly active antiretroviral therapy (HAART). This may suggest that the rapid improvement in the immune status of the patients taking antiretroviral therapy, may be masking any effect of selenium supplementation or adequate plasma selenium levels.

The majority of studies that investigated for a relationship between either plasma or serum selenium concentration or selenium supplementation and plasma HIV viral load, failed to find a significant association. Only one supplementation trial reported that selenium-responders had slower progression of HIV viral burden than the placebo or selenium non-responders group.

Selenium and mortality in HIV-infected subjects

Five studies evaluated the role of selenium on mortality in HIV-infected subjects. Allavena et al. analyzed the relationship between serum selenium levels in 80 HIV seropositive patients at stage IV of infection (CDC classification) treated with zidovudine (AZT) and mortality within one year. They observed that the patients who died had significantly lower selenium values. In a one-year prospective study on 95 HIV positive subjects, Constans et al. found that death was significantly associated with low serum selenium levels. Baum et al. longitudinally evaluated 125 HIV positive intravenous drug users for 3.5 years: selenium deficiency was significantly associated with mortality. In another study, Campa et al. observed 24 HIV positive children, for a five-year period and found that selenium deficiency was an independent risk factor for HIV-related mortality. Only one supplementation trial did not observe an effect of selenium on mortality.

Selenium and HIV co-infections

Only two studies have been carried out to investigate the relationship between selenium levels and co-infected HIV positive individuals. Look et al., in a cross-sectional study, compared serum selenium levels among HIV-infected patients co-infected with hepatitis C virus (HCV) and subjects infected with HIV only. HCV co-infected patients showed significantly lower selenium concentrations. Finally, Shor-Posner et al. demonstrated that lower levels of selenium significantly increased the risk of developing mycobacterial disease among HIV-infected individuals.

Selenium and cardiovascular involvement in HIV-infected subjects

Selenium seems to also play a role in the development of cardiac dysfunction among HIV-positive subjects. Two studies investigated this relationship and are described below.

Zazoo et al. prospectively evaluated the effect of selenium supplementation in 10 consecutive patients with both acquired immune deficiency syndrome (AIDS) and non-obstructive cardiomyopathy. Each patient received sodium selenite orally, 800 μg/day for 15 days and 400 μg/day for 8 days. Eight of these patients were found to have low plasma selenium levels before treatment yet six showed a return to a normal left ventricular shortening fraction within 21 days. One patient died on the 15th day of treatment and one had a thiamin deficiency.

Twagirumukiza et al. conducted a prospective multicenter study of 416 HIV positive Rwandan patients who were not receiving HAART and did not have a previously documented history of cardiovascular disease. Clinical examination, biochemical tests and echocardiography was carried out on all those enrolled in the study. Investigations showed that 71 (17.7%) patients had dilated cardiomyopathy and a low plasma level of selenium was significantly associated with the development of cardiomyopathy.

Selenium and hospital admissions in HIV infected subjects

A randomized, double-blind, placebo-controlled study evaluated the role of selenium supplementation on preventing hospital admission in patients with HIV infection, attending outpatient clinics. The trial showed a decrease in total hospital admission rates, percent of hospitalization and cost for hospitalization in the selenium-receiving group compared with the placebo group.

Discussion

Selenium is recognized to have an important role in both immunologic function and antioxidant defense mechanisms. Evidence suggests that oxidative stress contributes to the pathogenesis of HIV infection; in fact several studies have indicated that the apoptosis of CD4 cells contributing to HIV progression does not result solely from HIV infection, but largely from antioxidant imbalances in the host. It has been reported that selenium supplementation has a positive effect on oxidative stress in HIV-infected individuals. Moreover, studies show that selenium is vital to cell-mediated immunity and B-cell function.

According to the majority of published studies, HIV infection is associated with lower serum selenium concentration. Nutritional deficiencies are common in HIV-infected individuals and are caused by several factors: the oxidative state induced by the virus, malabsorption, altered metabolism, gut infection, altered gut barrier function, and the hypermetabolic state produced by chronic HIV infection. It has also been suggested that a possible cause of selenium depletion among HIV positive subjects is the utilization of selenium by HIV-1 virus to produce its own selenoenzymes.

In our literature review, three studies did not find a significant relationship between blood selenium concentrations when HIV seropositive and HIV seronegative subjects...
were compared. It is interesting to note that in a study conducted by Look et al., when comparing advanced stage HIV subjects with uninfected subjects, the former group had significant lower selenium levels. Whereas there was no difference in blood selenium levels if asymptomatic HIV-positive subjects were compared with uninfected subjects. These findings suggest that HIV infection alone is not the sole factor involved but perhaps it is the stage of disease that has a larger impact on selenium level.

Many authors report a significant relationship between CD4 cell count, opportunistic infections, HIV stage and selenium levels, whereas the association with HIV viral load is much more controversial.

Regarding the role of selenium in HIV-HCV co-infection, co-infected subjects usually have a higher levels of oxidative-stress which could explain the progressive lack of endogenous antioxidants and the subsequent decrease in selenium levels. As such, infection with more than one virus may cause an higher selenium depletion.

Data from the literature, indicates that cardiac tissue selenium levels are lower in AIDS patients with cardiomyopathy as compared to non-AIDS controls. Indeed, low plasma levels of selenium are associated with the development of cardiomyopathy in HIV positive individuals who are not receiving HAART. Two further studies showed an improvement of the patient’s left ventricular shortening fraction after selenium supplementation. The role of selenium in the pathogenesis of cardiac diseases has been suggested yet. Selenium deficiency has been strongly implicated in the pathogenesis of Keshan disease, a dilated congestive cardiomyopathy endemic to certain mountainous areas of China. A similar cardiomyopathy has been described in patients on long-term total parenteral nutrition who became selenium deficient. In conclusion, although HAART has remarkably improved the survival of HIV-infected individuals, selenium supplementation could yet have a role in slowing the disease progression, by reducing the incidence of opportunistic infections and HIV-associated mortality. This may have a particularly useful application in patients living in countries with poor economic resources. However, it is not possible to give an exact indication on the use of selenium in clinical practice.

The role of selenium in cardiovascular diseases seems interesting and deserve further investigations. Since the oxidative stress from free radicals may promote heart disease, selenium, because of its antioxidant properties, may help limit the oxidation of LDL cholesterol and thereby help to prevent coronary artery disease. A recent meta-analysis showed that selenium concentrations were inversely associated with coronary heart disease risk in observational studies but findings from randomized trials that addressed the cardiovascular efficacy of selenium supplementation are still inconclusive. HIV-positive patients, especially those living in resource replete settings, are now at greater risk of cardiovascular diseases, due to the effects of HAART and to the longer life-expectancy. The evaluation of the effect of selenium supplementation on cardiovascular risk among HIV-positive subjects, especially among those taking HAART, would be useful.

It is important to underscore that our study simply reviewed the available evidence on the effect of selenium in HIV infected subjects. Since we have not performed any statistical analysis we are not able neither to state the exact relationship between selenium and HIV disease nor to clearly define the role of selenium in the disease progression and the HIV-related mortality. Moreover published studies on this topic have several limitations. First, regarding selenium supplementation, only three randomized trials aimed to assess its effect on HIV viral load or CD4 count were performed. Most of included studies were cohort or case-control studies, with the known limitation of these studies. Second, in two trials, selenium was administered in association with other supplements, hampering the assessment of the effect due to selenium. Third, in most of included studies, an adjustment for principal confounders (i.e. CD4 count, HIV viral load, antiretroviral therapy, presence of factors that could reduce selenium adsorption) was not performed. Finally, several studies were performed in the era that preceded the introduction of highly active antiretroviral therapies or were conducted in resource poor settings, involving populations with limited or no access to HAART or patients taking non-standardised antiretroviral regimes.

Further randomized clinical trials, enrolling an adequate number of HIV infected subjects, are needed to clarify the role of selenium supplementation both in HIV naïve-patients and in those treated with HAART.

References

1. Fawzi WW, Msamanga GI, Spiegelman D, et al. A randomized trial of multivitamin supplements and HIV disease progression and mortality. N Engl J Med 2004;351:23-32.
2. Mehta S, Fawzi WW. Micronutrient supplementation as adjunct treatment for HIV-infected patients. Clin Infect Dis 2010;50:1661-3.
3. Selenium. Monograph. Altern Med Rev 2003;8:63-71.
4. Bellinger FP, Raman AV, Reeves MA, Berry MJ. Regulation and function of selenoproteins in human disease. Biochem J 2009;422:11-22.
5. Rayman MP. The importance of selenium to human health. Lancet 2000;356:233-41.
6. Vinceti M, Wei ET, Malagoli C, et al. Adverse health effects of selenium in humans. Rev Environ Health 2001;16:233-51.
7. Pitney CL, Royal M, Klebert M. Selenium supplementation in HIV-infected patients: is there any potential clinical benefit? J Assoc Nurses AIDS Care 2009;20:326-33.
8. Moreno-Reyes R, Suetsens C, Mathieu F, et al. Kashiin-Beck osteoarthropathy in rural Tibet in relation to selenium and iodine status. N Engl J Med 1998;339:1112-20.
9. Ge K, Yang G. The epidemiology of selenium deficiency in the etiological study of endemic diseases in China. Am J Clin Nutr 1993;57:5259-263.
10. Johnson RA, Baker SS, Fallon JT, et al. An occidental case of cardiomyopathy and selenium deficiency. N Engl J Med 1981;304:1210-2.
11. Chariot P, Bignani O. Skeletal muscle disorders associated with selenium deficiency in humans. Muscle Nerve 2003;27:662-8.
12. Lockitch G, Taylor GP, Wong LT, et al. Cardiomyopathy associated with non endemic selenium deficiency in a Caucasian adolescent. Am J Clin Nutr 1990;52:572-7.
13. Yusuf SW, Rehman Q, Casscells W. Cardiomyopathy in association with selenium deficiency: a case report. J Pain Parenteral Enteral Nutr 2002;26:63-6.
14. Cirelli A, Ciardi M, de Simone C, et al. Serum selenium concentration and disease progression in patients with HIV infection. Clin Biochem 1991;24:211-4.
15. Constans J, Pellegrin JL, Peuchant E, et al. Membrane fatty acids and blood antioxidants in 77 patients with HIV infection. Rev Med Interne 1993;14:1003.
16. Constans J, Pellegrin JL, Sergeant C, et al. Serum selenium concentration and disease progression in patients with HIV infection. J Acquir Immune Defic Syndr Hum Retrovirol 1995;10:392.
17. Look MP, Rockstroh JK, Rao GS, et al. Serum selenium, plasma glutathione (GSH) and erythrocyte glutathione peroxidase (GSH-Px)-levels in asymptomatic versus symptomatic human immunodeficiency virus-1 (HIV-1)-infection. Eur J Clin Nutr 1997;51:266-72.
18. Ndagefi F, Baribwira C, Coulter JB. Micronutrients and T-cell subsets: a comparison between HIV-infected and uninfected, severely malnourished Rwandan children. Ann Trop Paediatr 2007;27:269-75.
Review

McCullister K, et al. Impact of a selenium chemoprevention clinical trial on hospital admissions of HIV-infected participants. HIV Clin Trials 2002;3:483-91.

20. McClelland RS, Baeten JM, Overbaugh J, et al. Micronutrient supplementation increases genital tract shedding of HIV-1 in women: results of a randomized trial. J Acquir Immune Defic Syndr 2004;37:1657-63.

21. Hurwitz BE, Klaus JR, Llabre MM, et al. Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation: a randomized controlled trial. Arch Intern Med 2007;167:148-54.

22. Allavena C, Doussset B, May T, et al. Relationship of trace element, immunological markers, and HIV infection progression. Biol Trace Elem Res 1995;47:133-8.

23. Kupka R, Msamanga GI, Spiegelman D, et al. Selenium status is associated with accelerated HIV disease progression among HIV-1-infected pregnant women in Tanzania. J Nutr 2004;134:2556-60.

24. Kupka R, Garland M, Msamanga G, et al. Selenium status, pregnancy outcomes, and mother-to-child transmission of HIV-1. J Acquir Immune Defic Syndr 2005;39:203-10.

25. Baum MK, Shor-Posner G, Lai S, et al. High risk of HIV-related mortality is associated with selenium deficiency. J Acquir Immune Defic Syndr Hum Retrovirol 1997;15:370-4.

26. Campa A, Shor-Posner G, Indacochea F, et al. Mortality risk in selenium-deficient HIV-positive children. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20:508-13.

27. Kupka R, Mugusi F, Aboud S, 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;87:1802-8.

28. Boosalis MG. The role of selenium in chronic disease. Nutr Clin Pract 2008;23:152-60.

29. Gu BQ. Pathology of Keshan disease. A comprehensive review. Chin Med J 1983;96:251-61.

30. Djinji J, Thiabou G, Zirhi G, et al. Selenium deficiency and oxidative stress in asymptomatic HIV-infected patients in Côte d'Ivoire. Bull Soc Pathol Exot 2009;102:11-3.

31. Beck KW, Schramel P, Hedl A, et al. Serum trace element levels in HIV-infected subjects. Biol Trace Elem Res 1990;25:89-96.

32. Delmas-Beauvieux MC, Peuchant E, Couchouron A, et al. The enzymatic antioxidant system in blood and glutathione status in human immunodeficiency virus (HIV)-infected patients: effects of supplementation with selenium or beta-carotene. Am J Clin Nutr 1996;64:101-7.

33. Allard JP, Aghdassi E, Chau J, et al. Oxidative stress and plasma antioxidant micronutrients in humans with HIV infection. Am J Clin Nutr 1998;67:143-7.

34. Ogunro PS, Ogungbamigbe TO, Elemie PO, et al. Plasma selenium concentration and glutathione peroxidase activity in HIV/AIDS infected patients: a correlation with the disease progression. Niger Postgrad Med J 2006;13:1-5.

35. Tohill BC, Heilig CM, Klein RS, et al. Nutritional biomarkers associated with gynecological conditions among US women with or at risk of HIV infection. Am J Clin Nutr 2007;85:1327-34.

36. Khalili H, Soudbakhash A, Hajjabadolbaghi M, et al. Nutritional status and serum zinc and selenium levels in Iranian HIV infected individuals. BMC Infect Dis 2008;8:165.

37. Forrester JE, Wang XD, Knox TA, et al. Factors associated with serum retinol, alpha-tocopherol, carotenoids, and selenium in Hispanics with problems of HIV, chronic hepatitis C, and drug use. J Public Health Policy 2009;30:285-99.

38. Stephensen CB, Marquis GS, Douglas SD, et al. Gluthathione, glutathione peroxidase, and selenium status in HIV-positive and HIV-negative adolescents and young adults. Am J Clin Nutr 2007;85:173-81.

39. Henderson RA, Talusun K, Hutton N, et al. Serum and plasma markers of nutritional status in children infected with the human immunodeficiency virus. J Am Diet Assoc 1997;97:1377-81.

40. Maby DJ, Richard MJ, Arnaud J, et al. Relationship of plasma malondialdehyde, vitamin E and antioxidant micronutrients to human immunodeficiency virus-1 seropositivity. Clin Chim Acta 1994;224:89-94.

41. Constans J, Delmas-Beauvieux MC, Sergeant C, et al. One-year antioxidant supplementation with beta-carotene or selenium for patients infected with human immunodeficiency virus: a pilot study. Clin Infect Dis 1996;23:854-6.

42. Beck KW, Schramel P, Hedl A, et al. Serum trace element levels in HIV-infected subjects. Biol Trace Elem Res 1990;25:89-96.

43. Jones CY, Tang AM, Forrester JE, et al. Micronutrient levels and HIV disease status in HIV-infected patients on highly active antiretroviral therapy in the Nutrition for Healthy Living cohort. J Acquir Immune Defic Syndr 2000;36:4375-82.

44. Drain PK, Baeten JM, Overbaugh J, et al. Low serum albumin and the acute phase response predict low serum selenium in HIV-1 infected women. BMC Infect Dis 2006;6:85.

45. Baeten JM, Mostad SB, Hughes MP, et al. Selenium deficiency is associated with shedding of HIV-1-infected cells in the female genital tract. J Acquir Immune Defic Syndr 2001;26:360-4.

46. Rousseau MC, Molines C, Moreau J, Delmont J. Influence of highly active anti-retroviral therapy on micronutrient profiles in HIV-infected patients. Ann Nutr Metab 2000;44:212-6.

47. Look MP, Rockstroh JK, Rao GS, et al. Sodium selenite and N-acetylcysteine in anti retroviral-naive HIV-1 infected patients: a randomized, controlled pilot study. Eur J Clin Invest 1998;28:389-97.

48. Kelly P, Musonda R, Kaawembe E, et al. Micronutrient supplementation in the AIDS diarrhoea-wasting syndrome in Zambia: a randomized controlled trial. AIDS 1999;13:493-500.

49. Shor-Posner G, Miguez MJ, Pineda LM, et al. Impact of selenium status on the pathogenesis of mycobacterial disease in HIV-1-infected drug users during the era of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2002;29:169-73.

50. Zazzo JF, Chalas J, Lafont A, et al. Is nonobstructive cardiomyopathy in AIDS a selenium deficiency-related disease? JPN J Parenter Enteral Nutr 1988;12:537-8.

51. Twagirumukiza M, Nkeramihigo E, Semineba B, et al. Prevalence of diluted cardiomyopathy in HIV-infected African patients not receiving HAART: a multicenter, observational, prospective, cohort study in Rwanda. Curr HIV Res 2007;5:129-37.

52. Sandstrom PA, Murray J, Folks TM, Diamond AM. Antioxidant defenses influence HIV-1 replication and associated cytopathic effects. Free Radic Biol Med 1998;24:1485-91.

53. Kameoka M, Kimura T, Ikuta K. Superoxide enhances the spread of HIV-1 infection by cell-to-cell transmission. FEBS Lett 1993;331:182-6.

54. Droge W, Eck HP, Gmünder H, Mihm S. Requirement for prooxidant and antioxidant states in T cell mediated immune responses. Relevance for the pathogenetic mechanisms of AIDS? Klin Wochenschr 1991;69:1118-22.

55. Priis H, Kaestel P, Iverson A, Bugel S. Micronutrients and HIV infection. Boca Raton FL: CRC Press 2001; 183-200

56. Quercia RA, Korn S, O'Neill D, et al. Selenium deficiency and fatal cardiomyopathy in a patient receiving long-term home parenteral nutrition. Clin Pharm 1984;3:531-5.

57. Fleming CR, Lie JT, McCall JT, et al. [page 62] [Infectious Diseases Reports 2010; 2:e18]
Selenium deficiency and fatal cardiomyopathy in a patient on home parenteral nutrition. Gastroenterology 1982;83:689-93.

58. Tang AM, Forrester J, Spiegelman D, et al. Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2002;31:230-6.

59. Steinhart CR. HIV-associated wasting in the era of HAART: a practice-based approach to diagnosis and treatment. AIDS Read 2001;11:557-60, 566-9.

60. Grunfeld C, Kotler DP. Pathophysiology of the AIDS wasting syndrome. AIDS Clin Rev 1992:191-224.

61. Xu XM, Carlson BA, Grimm TA, et al. Rhesus monkey simian immunodeficiency virus infection as a model for assessing the role of selenium in AIDS. J Acquir Immune Defic Syndr 2002;31:453-63.

62. Shisler JL, Senkevich TG, Berry MJ, Moss B. Ultraviolet-induced cell death blocked by a selenoprotein from a human dermatotrophic poxvirus. Science 1998;279:102-5.

63. Dworkin BM, Antonecchia PP, Smith F, et al. Reduced cardiac selenium content in the acquired immunodeficiency syndrome. J Parenter Enteral Nutr 1989;13:644-7.

64. Constans J, Sire S, Sergeant C, et al. Dilated cardiomyopathy and selenium deficiency in AIDS. Apropos of a case. Rev Med Intern 1997;18:642-5.

65. Kavanaugh-McHugh AL, Ruff A, et al. Selenium deficiency and cardiomyopathy in acquired immunodeficiency syndrome. J Parenter Enteral Nutr 1991;15:347-9.

66. Flores-Mateo G, Navas-Acien A, Pastor-Barriuso R, Guallar E. Selenium and coronary heart disease: a meta-analysis. Am J Clin Nutr 2006;84:762-73.