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Research Article

# Relationship of Serum Zinc Level and Macro/Micronutrients with CD4 Levels in HIV Patients

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## Abstract

**Background:** Deficiencies of micronutrients increase the risk of various infections in HIV-infected patients. Zinc deficiency in HIV-infected patients may be associated with decreased CD4 cell counts.
**Objectives:** In this regard, the present study investigated the association between serum zinc levels, macro/micronutrient intake, and CD4 counts in HIV patients.
**Methods:** The research population of this study included 194 adult HIV patients aged 18 to 70 years referred to Shiraz Behavioral Diseases Center, Shiraz, Iran. The CD4 cell counts were extracted from patients' records. Serum zinc level was measured using atomic absorption method. Univariate and multivariate comparison of macro/micronutrient and food items with CD4 cells was performed using linear regression and SPSS20, and $P < 0.05$ was considered statistically significant.
**Results:** Fifty-seven percent were male, and the mean age and SD of total participants was 43.76 ± 9.06 years. The association between serum zinc levels and CD4 serum count is close to the significance level ($P = 0.05$), but the dietary zinc intake was not significantly correlated with serum CD4 counts ($P = 0.26$). Vegetable intake ($P < 0.001$) and fruits ($P = 0.01$) as well as absorption of vitamin A ($P = 0.002$), vitamin C ($P < 0.001$), beta-carotene ($P = 0.002$), folate ($P = 0.05$), and fiber ($P = 0.01$) from diet showed a direct and significant association with serum CD4 levels in HIV patients. Consumption of hydrogenated oils ($P = 0.04$) showed a significant inverse association with serum CD4 levels in these patients.
**Conclusions:** Evaluation of serum micro/macronutrients can play an essential role in the development of appropriate dietary and supplement guidelines provided by the healthcare system for HIV-infected patients, and it can influence the decision- and policy-making regarding the control of non-pharmacological management of these patients.

*Keywords:* Zinc, Macronutrient, Micronutrient, CD4, HIV

## 1. Background

The human immunodeficiency virus (HIV) is a retrovirus that infects cells with the CD4 marker and often causes immune system dysfunction within several years. The deficiency of the immune system is characterized by a decrease in $CD4^+$ lymphocyte levels. Although currently, HIV patients have a longer lifespan than in the past, the disease can predispose patients to other disorders. Nutritional therapy is among clinical care procedures for HIV patients. Developing and maintaining proper nutritional patterns can improve the function of the immune system in many cases. The enhancement of nutritional outcomes is possible by several means, including drug therapies to stimulate appetite and the use of supplements, and even the treatment of comorbid infections in these individuals. Proper nutrition has always been a challenge for these patients, especially those undergoing highly active antiretroviral therapy (HAART) therapy, and it often affects their morbidity and mortality. Weight loss, anorexia, nutrient malabsorption, diarrhea, and increased metabolism potentiate the risk of mortality in these patients (1). Many HIV-specific medications can cause nausea and diarrhea, which in turn leads to the loss of micronutrients. Patients with metabolic and nutritional disorders are prone to other inflammations, which, along with other immune reactions, affect nutritional status even more. Although it is not clear what deficiency in the diet increases a person's susceptibility to HIV infection, it is accepted that the progression of AIDS or improved response to antiviral drugs depends on a person's nutritional status. The deficiency of several micronutrients, known as "*hidden hunger*", which

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is especially common in sub-Saharan Africa, has been suggested as the pathogenesis of AIDS or its complications (2).

Micronutrients are essential for the stability of a functional immune system, and studies indicate that low levels of vitamin A and zinc in the serum affect the rate of HIV/AIDS conversion and early mortality in these patients (3). Micronutrient deficiencies are common in HIV patients. Studies show that micronutrient deficiencies, including vitamin D, vitamin A, zinc, and selenium, which have known roles in the immune system and infection prevention, are evident in these patients (4, 5).

The function of antioxidant mechanisms plays a major role in preventing the effects of free radicals and maintaining the patient's immune system. Antioxidants, including zinc and selenium as well as other free radical scavengers such as vitamins A, C, and E, are supplied through nutrition and nutritional supplements. Deficiency in micronutrients such as essential fatty acids, folate, zinc, and vitamin A can lead to mucosal damage and an increase in associated infections (6). Zinc deficiency in HIV-infected adults may increase mortality by decreasing CD4 count, enhancing the viral load, and increasing IgA (7). Zinc is an essential element for the development of the immune system in childhood, and it plays a critical role in the immune system function. Deficiencies of vitamins A, C, and E also lead to the suppression of different immune system cells. The importance of receiving enough macronutrients such as protein, energy along micronutrients for HIV patients is clear (1). So, diagnosing and correcting such deficiencies can be a solution to some problems of HIV patients. Proper nutrition and nutritional interventions may increase the life quality and expectancy of sufferers, improve the effectiveness of antiviral and other therapies, and reduce the risk of other diseases by improving body strength.

## 2. Objectives

To provide a proper dietary guideline for HIV-infected patients, it is necessary to evaluate their current diet plan and assess their serum levels of vitamins and minerals with implications regarding the immune system as well as their relationship with some markers of immune system status, including CD4. For this purpose, the present study aimed to investigate the correlation between macro/micronutrient intake, and serum zinc levels with CD4 count in HIV patients.

## 3. Methods

### *3.1. Participants*

The participants of this cross-sectional study were 194 adult patients aged 18 to 70 years referred to the HIV Voluntary Counseling and Testing Center (VCT) in Shiraz, Iran, and were selected by convenience sampling. The registered medical records in the VCT center were 1,804 cases with 1,335 active profiles. The records for HIV and AIDS patients who underwent pharmaceutical therapy with available CD4 count information for the past year were selected for evaluation. Table 1 lists the characteristics of the participants in the study. Exclusion criteria for this research included patients from the following groups: children, pregnant women, hospitalized and critically ill patients with severe depression. Patients whose daily energy expenditure was outside the range of 800 to 4,200 were also excluded from the study due to under/over report and ultimately, 194 patients were included in the investigation.

Abbreviation: SD, standard deviation.

### *3.2. Measurements*

Laboratory Measurements: CD4 cell count was extracted from patients' records. Serum zinc was measured using Atomic Absorption (AA500) Spectrometer using 5 cc blood samples from each participant, the reference amounts of 70 to 120 mcg/dL were considered the normal serum zinc.

General information questionnaire used in this research included age, gender, marital status, smoking, physical activity, the time elapsed since the onset of the disease or its diagnosis, prescribed medications, addiction used drugs if any, and income.

Food Frequency Questionnaire (FFQ) was a semi-quantitative questionnaire used in this study, consisting of 168 food items plus a standard measurement unit for each food item. Participants were asked to report their frequency of consumption of each food item within the last year based on the type of food in the form of daily (e.g., for bread), weekly (e.g., for meat or vegetables), or monthly (e.g., for fish). Then, individuals' daily intakes were calculated separately, in grams per day for each food item, using the home scale guideline. The energy content of the items in the FFQ was also calculated using the USDA Department of Food Ingredients (available (available in the Nutritionist 4.0 software). The table of local food ingredients was used for some traditional Iranian food items that were not available in the software, including local bread and some dairy products like curd.

**Table 1.** Relationship Between HIV Patient Profiles and Serum CD4 Levels

| Participants Characteristics | Mean ± SD/No. (%) | Standardized Coefficients (Beta) | P-Value |
|---|---|---|---|
| **Age, y (n = 190)** | 43.76 ± 9.06 | -0.24 | 0.001 |
| **Weight (kg) (n = 191)** | 63.65 ± 12.85 | 0.21 | 0.002 |
| **Disease duration, y (n = 180)** | 7.42 ± 5.18 | -0.05 | 0.49 |
| **Serum zinc (mg/dL) (n = 193)** | 91.18 ± 34.42 | - | - |
| Deficiency < 72.6 | 83 (43.3) | | |
| Normal 72.6 - 127 | 83 (43.3) | | |
| Higher > 127 | 27 (13.4) | | |
| **CD4 (n = 193)** | 455.96 ± 296.97 | - | - |
| < 500 | 98 (50.8) | | |
| ≥ 500 | 95 (49.2) | | |
| **Gender (n = 194)** | | -0.30 | < 0.001 |
| Male | 110 (56.7) | | |
| Female (ref) | 84 (43.3) | | |
| **Marital status (n = 194)** | | 0.08 | 0.26 |
| Single | 48 (24.7) | | |
| Married | 92 (47.4) | | |
| Divorced | 54 (27.8) | | |
| **Education (n = 192)** | | 0.16 | 0.02 |
| Illiterate | 6 (3.1) | | |
| Primary | 70 (36.5) | | |
| Intermediate | 64 (33.3) | | |
| Diploma | 44 (22.9) | | |
| Bachelor | 7 (3.6) | | |
| Master | 1 (0.5) | | |
| **Employment (n = 194)** | | 0.17 | 0.01 |
| Yes | 85 (43.8) | | |
| No | 109 (56.2) | | |
| **Smoking (n = 194)** | | -0.16 | 0.02 |
| Yes | 100 (51.5) | | |
| No (ref) | 94 (48.5) | | |
| **Drug user (n = 194)** | | -0.262 | < 0.001 |
| Yes | 45 (23.2) | | |
| No (ref) | 149 (76.8) | | |
| **Physical activity (n = 194)** | | 0.02 | 0.06 |
| Very low | 89 | | |
| Low | 53 | | |
| Moderate | 44 | | |
| Severe | 8 | | |
| **Hepatitis C (n = 191)** | | -0.26 | < 0.001 |
| Yes | 88 (46.1) | | |
| No | 103 (53.9) | | |
| **Hepatitis B (n = 189)** | | -0.20 | 0.004 |
| Yes | 14 (7.4) | | |
| No | 175 (92.6) | | |

### 3.3. Statistical Analysis

Kolmogorov-Smirnov test was used to evaluate the normality of data distribution before choosing any statistical test for quantitative variables. Linear regression was used for the univariate and multivariate comparison of the correlation between macro/micronutrients, and different food items with CD4 count. All analyses were performed using SPSS ver.20, and $P < 0.05$ was considered statistically significant.

## 4. Results

The present study was performed with the participation of 194 patients, of which 57% (n = 110) were men and 43% (n = 84) were women with the mean age and standard deviation (SD) of 43.76 ± 9.06 years. The mean serum level of zinc was 91.18 ± 34.42, while the mean count of CD4 cells in the serum of participants was 455.96 ± 296.97 (Table 1). The mean of dietary zinc was 10.13 ± 4.09 (Table 2).

The zinc intake from food did not show a significant correlation with CD4 serum levels ($P = 0.26$) (Table 2). However, a significant correlation was found for using fruits ($P = 0.01$) and vegetables ($P < 0.001$) with CD4 count in HIV patients (Table 2). The findings for consumption of dietary hydrogenated oils ($P = 0.04$) showed a significant inverse correlation with serum CD4 levels in these patients (Table 2). The amount of dietary vitamins A ($P = 0.002$), C ($P < 0.001$), beta-carotene ($P = 0.002$), folate ($P = 0.05$), and fiber ($P = 0.01$) had a significant and direct correlation with serum CD4 counts (Table 2).

Table 3 presents the information regarding zinc and CD4 levels correlations in patients' serum, taking into account the confounding factors. In the 1st model, the correlation between serum zinc and serum CD4 levels was close to significant ($P = 0.05$), disregarding the confounding variables; this model demonstrated that a 1-unit increase in serum zinc levels might increase CD4 levels by 0.4 units. In the second model, variables with a P-value lower than 0.2 in the analysis were included in multivariate analysis, and the serum zinc levels did not show a significant correlation with CD4 levels after including confounders in the analysis. Age and weight had a significant correlation with CD4 levels in multivariate analysis. With increasing one unit in age, CD4 level is expected to decrease by 0.172 unit ($P = 0.01$), while one unit increase in weight increases CD4 levels by 0.225 unit ($P = 0.001$).

## 5. Discussion

The present cross-sectional study investigated the dietary intake of zinc and various vitamins and their effects on serum CD4 levels. The findings showed that only fruits and vegetables had a direct and significant correlation with serum CD4 counts among various food groups ($P \leq 0.05$). Oils also showed a significant inverse correlation with CD4 counts in this study ($P \leq 0.05$). Serum zinc levels of HIV patients had a significant correlation with their CD4 levels, but it was not significant. Confounding variables were included in the model (Table 3). Despite the frequency of research on this issue, there are conflicting results regarding the correlation between serum and dietary zinc levels with CD4 counts. In a study by Jones et al., the levels of micronutrients, including zinc, did not show a significant correlation with $CD4^+$ cell counts (3). However, other studies show a significant correlation between them. In their study, Soudbakhsh et al. observed a statistical correlation between serum zinc levels and $CD4^+$ cell counts (8). Decreased serum zinc levels in HIV patients have been confirmed in other studies. In a study by Rayman, HIV patients, and drug users, a decrease in serum zinc levels is indicated (9). The decreased levels of serum zinc in 23% of HIV patients in association with lower CD4 counts have been demonstrated in a study by Wellinghausen et al. (10). The findings of the present study indicate that 43% of the subjects have suboptimal serum zinc levels, while 46% have a CD4 serum count lower than 500. The prescription of vitamin supplements and micronutrients seems necessary in these patients. Some studies have examined the implications of supplementation and its effect on boosting the immune systeam.

A randomized controlled trial on 231 HIV patients with low serum zinc levels was performed by Baum et al. In this study, zinc supplementation (12 mg daily for women and 15 mg daily for men) for 18 months was considered for patients, and the efficacy of this strategy was evaluated regarding the course of HIV disease. Based on CD4 count analysis, the zinc supplementation approach reduced immunological failure four times more than other patients. However, the viral load was not affected by supplementation and did not change the mortality rate compared to other patients. Overall, from the findings of Baum's study, it appears that long-term supplementation with zinc at the nutritional level delays immunological failure (11). Inconsistent with these findings, many studies indicate that micronutrient supplements such as zinc, selenium, and vitamins A, C, and E cannot effectively reduce mortality in HIV patients or prevent other diseases in them (12).

The identified correlations for serum zinc levels in HIV patients suggest that parallel to disease progression, both zinc levels, and CD4 cell counts descend, and it may support the hypothesis of a causal relationship between zinc and immunity; however, our results were not consistent with the hypothesis. Our findings also showed that the levels of vitamins A, C, and beta-carotene have a direct and significant correlation with CD4 serum levels. Some studies have examined adjuvant supplementation and its effect on the HIV disease course based on CD4 levels.

**Table 2.** Relationship Between Macronutrient Intake, Micronutrients, and Food Intake with Serum CD4 Levels

| Macronutrients | Intake, Mean ± SD | Standardized Coefficients (Beta) | P-Value |
|---|---|---|---|
| **Protein (g/day)** | 76.78 ± 31.37 | 0.04 | 0.51 |
| **Fat (g/day)** | 73.16 ± 36.36 | 0.01 | 0.86 |
| **Energy (kcal/day)** | 2341.46 ± 865.72 | 0.04 | 0.51 |
| **Micronutrients** | | | |
| Zinc (mg/d) | 10.13 ± 4.09 | 0.07 | 0.26 |
| Magnesium (mg/d) | 380.82 ± 156.92 | 0.10 | 0.15 |
| Iron (mg/d) | 16.61 ± 6.56 | 0.07 | 0.31 |
| Vitamin A (mcg/d) | 951.69 ± 633.36 | 0.22 | 0.002 |
| Vitamin C (mg/d) | 165.44 ± 120.84 | 0.27 | < 0.001 |
| Vitamin E (mg/d) | 18.95 ± 14.43 | 0.04 | 0.54 |
| Folate (mcg/d) | 462.70 ± 202.76 | 0.13 | 0.05 |
| Selenium (mcg/d) | 0.04 ± 0.025 | 0.09 | 0.19 |
| Beta-carotene (mg/d) | 979.05 ± 581.25 | 0.21 | 0.002 |
| Dietary fiber (g/day) | 25.92 ± 12.21 | 0.17 | 0.01 |
| **Food items** | | | |
| Red meat (g/day) | 21.73 ± 30.75 | 0.07 | 0.26 |
| Organ/high fat Meat (g/day) | 19.45 ± 32.45 | -0.04 | 0.54 |
| Chicken (g/day) | 21.84 ± 17.08 | -0.03 | 0.63 |
| Fish (g/day) | 10.68 ± 19.56 | 0.06 | 0.31 |
| Egg (g/day) | 32.49 ± 33.75 | 0.11 | 0.08 |
| Nuts (g/day) | 8.87 ± 30.81 | 0.00 | 0.96 |
| Soybeans/legums (g/day) | 69.14 ± 60.83 | 0.04 | 0.47 |
| Fast food (g/day) | 6.72 ± 15.18 | -0.10 | 0.13 |
| Vegetable (g/day) | 344.57 ± 226.79 | 0.25 | < 0.001* |
| Fruits (g/day) | 385.31 ± 323.51 | 0.16 | 0.01* |
| Dairy (g/day) | 156.32 ± 122.50 | 0.02 | 0.70 |
| Fatty dairy (g/day) | 43.66 ± 83.95 | -0.09 | 0.15 |
| Hydrogenated oil (g/day) | 5.99 ± 12.12 | -0.13 | 0.04* |
| Sugary food and snacks (g/day) | 68.90 ± 66.44 | 0.11 | 0.09 |
| Salty food and snacks (g/day) | 18.74 ± 15.86 | 0.05 | 0.41 |

The dietary intakes were assessed using a food frequency questionnaire in a cross-sectional study by Karimi et al. on 48 HIV patients. Although the study did not show a deficiency in micronutrients, deficiency of folate, B12, and vitamin E was demonstrated in female HIV patients. The results for the correlation of vitamins and minerals with CD4 levels were not significant for any of the micronutrients (zinc, iron, folate, vitamins A, C, E) (13).

Bilbis et al. investigated the serum levels of antioxidant vitamins (vitamins A, C, E) and minerals (zinc, iron, and copper) in 90 HIV patients. They found that serum levels of micronutrients significantly correlated with CD4 count (14). The antioxidant vitamin levels in HIV patients were lower than that of non-HIV individuals, and these levels, as well as zinc and iron levels, showed a positive correlation with the level of $CD4^+$ cells in the serum of HIV patients (13).

Hendricks et al. examined the association between dietary patterns and changes in body mass index (BMI), CD4 count, and viral load in 348 male HIV patients based on a 3-day dietary record. Three dietary patterns were identi-

**Table 3.** Relationship Between Serum Zinc and CD4 Considering Confounders

| Factors | Standardized Coefficients (Beta) | P-Value |
|---|---|---|
| **Model 1, serum zinc** | 0.44 | 0.05 |
| **Model 2, serum zinc** | 0.09 | 0.18 |
| **Age** | -0.17 | 0.01 |
| **Weight** | 0.22 | 0.001 |
| **Education** | 0.12 | 0.09 |
| **Gender (male:female)** | -0.19 | 0.05 |
| **Employment (yes:no)** | 0.06 | 0.44 |
| **Smoke (yes:no)** | -0.04 | 0.59 |
| **Drugs (yes:no)** | -0.08 | 0.32 |
| **Physical activity (yes:no)** | 0.09 | 0.19 |
| **HCV (yes:no)** | -0.05 | 0.51 |
| **HBV (yes:no)** | -0.13 | 0.05 |

Abbreviations: HCV, the hepatitis C virus; HBV, the hepatitis B virus.

fied as juices and carbonated beverages, fast foods and fruit beverages, and low-fat dairy products, fruits, and vegetables. Participants in the fast food and fruit drinks group had the lowest fiber intake, the highest viral load, and the lowest CD4 count, while subjects in low-fat dairy products, fruits, and vegetables, showed higher protein, dietary fiber, and micronutrients intake with the highest BMI and CD4 count (15). Serum zinc levels are also reduced in some diseases, including tuberculosis and toxoplasma infection, which emphasize the impact of diseases on the immune system and the role of zinc in boosting the immune system. Due to zinc's affinity with integrase inhibitors, some medications used for AIDS treatment also interfere with zinc absorption. So, these items could not be included in the model in multivariate analysis.

Although numerous studies have demonstrated the correlation between zinc levels and CD4 count, such a correlation was not found in a study by Jones et al. and also the present study (3). Similar to our study, the zinc levels in all of these studies were measured by the standard atomic absorptiometry method. However, merely based on observational studies, one cannot reach a definite and reliable conclusion about the effect of zinc on the immune system, and a randomized controlled trial (RCT) is necessary to achieve more reliable results. Where there would be a possibility for checking the effect of all micronutrients involved in boosting the immune system, it can provide a complete nutritional analysis for these patients. In the present study, we have tried to cover as accurate as possible calculations of food intake using valid food intake questionnaires for these patients.

### *5.1. Conclusions*

The investigation of the micronutrients that are most likely to improve the immune system of HIV patients and their correlations with an immune system marker such as CD4 plays a critical role in the preparation of an appropriate dietary plan or packages and supplements by the healthcare system. It may also have implications in decision- and policy-making to manage these patients.

## Footnotes

**Authors' Contribution:** Study concept and design: P. K, H. J., and A. S.; Analysis and interpretation of data: P. K. and B. I.; Drafting of the manuscript: B. I. and A. S.; Critical revision of the manuscript for important intellectual content: P. K., H. J., and A. S.; Statistical analysis: B. I., P. K., and A. S.

**Conflict of Interests:** This study was funded (ID: 22239) by Shiraz University of Medical Sciences, Shiraz, Iran and there is no personal financial interest in this research. The patent has been filed and issued. There is no unpaid consultation fee or stocks or shares in companies. Personal or professional relations with organizations and individuals (parents and children, wife and husband, family relationships, etc.). There is no unpaid membership in a government or non-governmental organization. Parisa Keshani is one of the editorial board members of this journal.

**Data Reproducibility:** The data presented in this study will be available to the reviewers or the EIC upon their request without any limitation as a part of the review process.

**Ethical Approval:** This study is approved under the Ethical approval code of IR.SUMS.REC.1400.133.

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**Informed Consent:** Written informed consent was obtained.

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