Conjecturas

DOI: 10.53660/CONJ-165-303

Zinc-enriched cookies improve immunity and decrease the incidence of opportunistic diaseases in AIDS patients

Biscoitos enriquecidos com zinco melhoram a imunidade e diminuem a incidência de doenças oportunistas em pacientes com AIDS

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RESUMO

Introdução: a Síndrome da Imunodeficiência Adquirida (AIDS) é um grupo de afecções surgidas devido à falha do sistema imunológico do hospedeiro. **Métodos:** o estudo foi realizado entre 2015 e 2016 com pacientes atendidos em um Centro Especializado em Doenças Infecciosas Parasitárias do Paraná. Zinco foi adicionado à formulação de um biscoito afim de suplementar a alimentação dos pacientes com 20 mg Zinco/dia. A pesquisa foi dividida em duas etapas, para avaliar, no tempo 0 e após 3 meses de suplementação, o efeito sobre a contagem de células TCD4+ e na Carga Viral (CV) em organismo de pacientes com AIDS. Na etapa 1, 51 pacientes saudáveis foram submetidos a um questionário para obtenção de dados antropométricos e socioeconômicos, de estado de saúde e realização de exames de sangue. Os pacientes receberam biscoitos suplementados com zinco em quantidade suficiente para três meses. Na etapa 2, 18 pacientes saudáveis foram submetidos novamente à avaliação antropométrica, questionados sobre o consumo do biscoito, o estado de saúde, além da contagem de TCD4+ e CV. **Resultados:** a análise dos dados não mostrou diferença estatística na CV; no entanto, a suplementação promoveu um aumento significativo na contagem de TCD4+. Além disso, houve diminuição significativa na incidência de doenças oportunistas durante o período de suplementação. **Conclusão:** a suplementação com zinco sugere ser promissora para elevar a contagem de células TCD4+, colaborando positivamente para uma resposta imunológica mais eficiente e melhora na percepção de qualidade de vida.

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Palavras-chave: minerais; suplemento alimentar; biscoitos; HIV; sistema imunológico.

ABSTRACT

Introduction: Acquired Immunodeficiency Syndrome (AIDS) is a group of conditions that arise due to the failure of the host's immune system. **Methods**: the study was carried out between 2015 and 2016 with patients treated at a Specialized Center for Parasitic Infectious Diseases in Paraná. Zinc was added to the formulation of a biscuit in order to supplement the patients' diet with 20 mg Zinc/day. The research was divided into two stages, in order to evaluate, in time 0 and after 3 months of supplementation, the efect on TCD4+ cell count and on the Viral Load (VL) in the body of AIDS patients. In step 1, 51 healthy patients were submitted to a questionnaire to obtain anthropometric and socioeconomic data, their health status and blood tests. Patients received enough zinc supplemented biscuits for three months. In step 2, 18 healthy patients were again submitted to anthropometric assessment, asked about the consumption of the biscuit and health status, in addition to the TCD4+ and VL counts. **Results**: data analysis showed no statistical difference in VL; however, supplementation promoted a significant increase in TCD4+ count. Furthermore, there was a significant decrease in the incidence of opportunistic diseases during the supplementation period. **Conclusion**: zinc supplementation suggests to be promising to increase the TCD4+ cell count, contributing positively to a more efficient immune response and improvement in the perception of quality of life.

Key-words: minerals; food supplement; biscuits; HIV; immune system.

INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is the name given to the set of opportunistic diseases arising from the process of weakening the immune system mediated by the Human Immunodeficiency Virus (HIV) (LU et al., 2018; HEMELAAR et al., 2019). Epidemiologically, AIDS translates as a global epidemic that extends in three ways around the globe: the nascent epidemic, which corresponds to countries where the prevalence of HIV infection is less than 5% in all subpopulations with high behavior and risk of exposure to the virus. The concentrated epidemic, countries where the prevalence of HIV infection is over 5% in one or more subpopulations with high-risk behavior; and the generalized epidemic, which occurs in countries where HIV infection is no longer restricted only to subpopulations of risky behavior (LAZZAROTTO et al., 2010; SOARES, ARMINDO, ROCHA, 2014; BELOUKAS et al., 2016; HEMELAAR et al., 2019; READ et al., 2019). It is estimated that there are already more than 35 million infected with HIV (MOREIRA; CHIARELLO, 2008; WHO, 2017).

Once the host has contact with the virus, whether through sexual, parenteral, transfusion or other ways in which blood or secretions are shared, the infection will start from the contact and invasion of the host's immune system cells by HIV (LAZZAROTTO et al., 2010; SOARES, ARMINDO, ROCHA, 2014). HIV mainly infects T helper cells (T helper cells) of the specific group number 4 or TCD4+. TCD4+ cells are responsible for modulating the immune response and its surface phenotypic marker, the CD4+ receptor, has great affinity with the gp120 protein in the HIV viral envelope (ROBBINS et al., 2001; PARHAM, 2011).

The interaction of TCD4+ lymphocyte with the HIV gp120 protein triggers the mechanism of lymphocytic invasion by the virus. The success of HIV in invading the immune system is due to the enzymatic framework of the virus. Compulsory intracellular parasite, HIV requires cellular machinery for replication, which includes cellular enzymes, structures and missing elements for the virus (BRITO, CASTILHO, SZWARCWALD, 2001; PARHAM, 2011; SOARES, ARMINDO, ROCHA, 2014). Through the enzyme reverse transcriptase, HIV promotes the transformation of its own RNA into DNA. Viral proteases break the bonds between amino acids and integrases promote the fusion of viral DNA with the host's DNA, a mechanism by which the virus assumes the cellular machinery in favor of viral replication. Thus, when viral replication begins, there is depletion of TCD4+ lymphocytes and cell apoptosis, compromising the host's immune response to various etiologic agents (BRITO, CASTILHO, SZWARCWALD, 2001; PARHAM, 2011; SOARES, ARMINDO, ROCHA, 2014; LU et al., 2018).

The body's immune response becomes more deficient as HIV advances on the immune system. Additionally, immunocompetence is impaired if there is nutritional deficiency, which implies a deficient functioning of cellular structures, formation of proteins, enzymes and cells. Among the most common complications in infected patients are changes in taste and appetite, weight loss, alopecia, diarrhea, chronic weakness and deleterious psychological consequences. The loss of micronutrients is vitally important for the proper functioning of the organism (KAISER et al., 2006; ASDAMONGKOL, PHANACHET, SUNGKANUPARPH, 2013). In this sense, Zinc (Zn) is a micronutrient involved in the activity of more than 300 enzymes, participating constitutively on synthesis and degradation of carbohydrates, lipids and proteins. Zinc collaborates in the functioning of the antioxidant defense, sensorineural function and in

correct functioning of the immune system (KAISER et al., 2006; ASDAMONGKOL, PHANACHET, SUNGKANUPARPH, 2013; DIRAJLAL-FARGO et al., 2019; READ et al., 2019).

Zinc is closelly related to the cells of the immune system, since it is involved in the translation, transport and replication of DNA. In addition, Zinc can affects the phagocytosis process of macrophages and neutrophils, interfering with cell lysis mediated by killer cells and cytolytic action of T cells. In T cells, zinc is part of enzymes such as 5'NT (ecto-5'-nucleotidase), present in the cell membrane of these cells (the zinc finger nucleases) (KAISER et al., 2006; PARHAM, 2011; ASDAMONGKOL, PHANACHET, SUNGKANUPARPH, 2013; GNATIENKO et al., 2018; DIRAJLAL-FARGO et al., 2019; READ et al., 2019).

Zinc deficiency is an aggravating factor for the progression of AIDS, since the deficiency of this mineral is present in all stages of the syndrome and is a factor that contributes to the increase in viral replication (GNATIENKO et al., 2018; DIRAJLAL-FARGO et al., 2019;).

In AIDS patients, zinc deficiency impairs the immune system's already weakened response. The use of this mineral could be a complementary alternative for the treatment of AIDS. Therefore, this study aimed to assess the effects of supplementation with zinc-enriched biscuits on general well-being, symptoms, TCD4+ cell count and viral load (VL) of patients diagnosed with AIDS at the Specialized Center in Parasitic Infectious Diseases (CEDIP), from the city of Cascavel, Paraná, Brazil.

METHODS

Selection of participants

The present study is a longitudinal cohort. After approval by the ethics committee under number 33713113.0.0000.5564. The inclusion criteria were: individuals of both sexes (n=37) aged between 21 and 50 years diagnosed with AIDS; CD4+ cell count below 300 cells/mm^3. A random selection of patients who attended the inclusion criteria was performed. The selected patients who wished to participate in the study signed a Free and Informed Consent Form (ICF). Patient´s interview and health

evaluations occurred at the beginning of the study (Step 1) and 3 months after the first assessment (Step 2).

Formulation of the biscuit enriched with zinc

The study of Teixeira et al. (2018) was used as a reference for the preparation of biscuits enriched with zinc. A biscuit-based formula consisting of eggs, refined sugar, baking powder, cocoa, butter, wheat flour, rice flour, bean flour and chelated zinc at an approximate amount of 3.3 mg of zinc per biscuit was developed.

Data collection from research participants

The patients attended CEDIP from February 2015 to December 2016. In step 1 of the study, the personal, sociodemographic and health status data of the patients were assessed through a targeted questionnaire. Data of VL and TCD4+ cells (CD4+) count registered on archived medical records of each participant constituted the data used in Step 1. Laboratory conducted the measuring of Plasma zinc levels of the participants, before and after supplementation. Participants underwent nutritional status assessment using body weight and height measurements to classify their body mass index (BMI). At the end of step 1, the colaborators of study instructed participants regarding of consume of six cookies enriched with zinc (approximately 20 mg of Zn/day) during the day, for a period of 3 months.

In step 2, after three months of consumption of the cookies, a new questionnaire was applied to re-assess the health status and verify the cookie consumption; the assessment of nutritional status was repeated and the data of VL and TCD4+ cell count updated, when possible.

Blood collection techniques and instrument

Blood samples were collected from the participants to determine plasma zinc levels. For this procedure, laboratorists used surgical gloves, tourniquet, 70% alcohol, cotton, dressings, EDTA tubes, 10 mL syringes and disposable needles.

Determination of blood zinc levels

To determine zinc levels, were necessary pre-digest samples with approximately 500 mg of blood with 6 mL of bidistilled nitric acid (Merck) in open

vessels, by conventional heating. After cooling, the digestions were diluted with ultrapure water to 50 mL in a polypropylene container.

To detect zinc values, an inductively coupled plasma optical emission spectrometer (ICP-OES) with axial vision configuration (SpectroCiros CCD, Spectro Analytical Instruments, Germany) was used. The complete methodology applied to zinc determination is described according to Tonel et al. (2018).

Data analysis

To compare the parameters before and after supplementation with the biscuit, paired t test was perfomed using Prism 7.01 software, considering a statistically significant difference if $p<0.05$. In addition, possible correlations between VL and CD4+ cells, the duration of the disease and the number of opportunistic diseases were verified using the multiple linear regression test.

RESULTS

In step 1 of the study, the participation of 51 volunteers who attended CEDIP, a specialized center in Cascavel-PR, from 2015 to 2016 was recorded. The general data of participants are shown in Chart 1.

Chart 1 General data of participants in step 1 of the study.

Data		Min - max
Age (years)		30 – 54
Number of daily meals		2 – 5
Daily water ingestion (liters)		0.78 – 3.00
Time of disease discover (years)		0.1 – 12.00
Sex	Female	n = 24 (47.06 %)
	Male	n = 27 (52.97%)
Detection by blood test		n=36 (70.60%)
Contraction through unprotected sex		n= 34 (66.60%)

Apetite	Good	n=37 (72.55%)
	Regular	n=12 (23.53%)
	Bad	n=2 (3.92%)

The descriptive data demonstrate a median age of 42 years and 36 months of disease diagnosis, mostly by routine blood tests (70.60%). Regarding eating habits, most patients rated their appetite as good, with adequate water ingestion, and an average of 4.00 daily meals and 1.50 liters water/day.

In step 2, 18 of the initial 51 participants answered the questionnaire and performed the assessment of nutritional status. Almost 100% of patients who ate the zinc-enriched biscuits relished the biscuit received, and only 1 (5.56%) patient reported gastrointestinal discomfort after consumption. Regarding the time stipulated for biscuit consumption, 1 (5.56%) patient did not consume all of the biscuits and 3 (16.67%) reported consumption in less than 3 months.

Although there is no statistical significance at IMC, Plasmatic Zinc levels and VL before and after supplementation, the number of opportunistic diseases was significantly lower and CD4+ cell counts significantly increased (Table 1). When asked about changes in their clinical condition, 11 patients (61.1%) observed improvements such as greater disposition, stronger hair and nails, and improved immunity.

Table 1 Changes observed in blood, nutritional and clinical parameters of AIDS patients after the consumption of cookies supplemented with zinc.

Parameter	**Before supplementation (Min - max)**	**After supplementation (Min - max)**	**p**
Viral Load (cells/mm³) (n=24)	47.00 - 1636.00	43.00 - 1345.00	0.4609
TCD4+ count (copies/mL) (n=24)	65.00 - 533.00	134.00 - 543.00	0.0003*
IMC (kg/m²) (n=17)	18.13 – 41.12	19.61 – 42.64	0.3060

Number of opportunistic diseases (n=18)	6 - 12	1 - 17	0.0027*
Plasmatic zinc (mg/L) (n=33)	0.82 - 2.74	0.80 - 2.67	0.8207

*The p value was considered as statistic significant if $p < 0.05$.

DISCUSSION

The results of the present study revealed that Zn supplementation was not able to decrease the viral load, considering the supplementation provided and the proposed treatment time. This result was similar to obtained by Dirajal-Fargo et al. (2019), where a zinc supplementation with 11 mg/day was not capable to demonstrate a reduction in number of HIV copies. It is possible that, because of your kinetics, zinc was not properly distributed among structures and proteins components of immune framework due to nutritional deficiency of plasmatic proteins or zinc sequestration in cells of immune system (SWINGLER et al., 2007; XU et al., 2008; RAYMOND et al., 2010; READ et al., 2019).

In addition to being present in the structure of more than 300 enzymes, Zinc participates in synthesis and degradation processes, in transcription and translation of polynucleotides, and in the correct functioning of immune system proteins (DIRAJLAL-FARGO et al., 2019; OLENDER et al., 2012). These proteins are directly involved in the genome editing process, adding or removing base pairs as needed. Therefore, zinc can be implicated in all aspect of viral life cycle, inhibiting retrovirus such as HIV. Contradictorily, when *in vivo*, HIV stimulates zinc influx to macrophages, retarding death of this cells and then, it can remain latent and viable until ceases the antiretroviral treatment. Zinc sequestration in some cells of immune system or zinc deficiency usually observed in HIV-infected patients prejudice the formation of immune system proteins, determining impaired immune response. The lack of responsiveness of immune system determines the surging of opportunistic diseases (XU et al., 2008; AFFONSO et al., 2012; OLENDER et al., 2012; GNATIENKO et al., 2018; DIRAJLAL-FARGO et al., 2019).

The number of opportunistic diseases decreased significantly after zinc supplementation with 20 mg/day, fact observed in other zinc supplementation studies as

well (GNATIENKO et al., 2018; DIRAJLAL-FARGO et al., 2019; READ et al., 2019). The diminishing in comorbidities ameliorate the well-being in most patients, which related general health status improvement, including more disposition to daily activities, stronger hair and nails. This data are corroborated by the study carried out by Sneij et al. (2016), which demonstrated a correlation between zinc levels and the emergence of opportunistic diseases.

The depletion of immune cells mediated by lack of maintenance of the necessary components for a correct activity of the defense system is closely related to the cellular processes that support responses to invaders, causing more or less opportunistic diseases (DIRAJLAL-FARGO et al., 2019; READ et al., 2019). A study by Caza et al., (2016) demonstrates that cellular machinery tends to response failure against opportunistic diseases such as fungal meningoencephalitis, caused by *Cryptococcus neoformans* when there is a lack or malfunction of zinc finger proteases.

With an adequate offer of food and the improvement of well-being, not only do levels of zinc improve, but the calorie intake also enables constitutional elements to form, such as zinc finger nucleases (KAISER et al., 2006; ASDAMONGKOL et al., 2013). A study published by Olender et al. (2012) demonstrated the role of zinc finger nucleases on the multiplication of TCD4+ lymphocytes, retarding HIV progression and contributing to a better quality of life. The supplementation of 20 mg/day proposed by this study was capable of promoting a significant increase in TCD4+ cell counts, in agreement with other authors (READ et al., 2019; DIJARAJLAL-FARGO et al., 2019; GNATIENKO et al., 2018; SNEIJ et al., 2016).

In our experiment, zinc before and after supplementation was in superior limit range for this parameter in humans (50 – 170 mg/dL) and it was not possible observe an increase in concentration of plasmatic zinc. Higher blood zinc concentrations were also found in a study conducted by Tang et al. (1993), suggesting that zinc levels are associated with HIV progression. In HIV-infected patients, excesses of zinc indicate an acceleration in disease; however, the zinc sequestration in liver and other cells of these patients are not determinants of tissue toxicity. Thus, it is supposed that as zinc binds in structures of serum proteins, it leaves blood flow to enter in natural reservoirs. It is possible deduce that a lack of structures that zinc could make a constitutional part may cause an increase blood levels, when patient is supplemented only with this microelement.

The clinical improvement reported by most patients in this study can be correlated with the reduction of some biological markers. Dijaeajlal-Fargo et al. (2019) evaluated inflammation markers in the serum of HIV-positive patients before and after zinc supplementation. Even though they administered a zinc concentration which was lower than that applied in this study, the decrease in inflammation marker levels was statistically relevant. Besides that, Gnatienko et al. (2018) demonstrated an improvement in mortality biomarkers after zinc supplementation, via a reduction in coronary heart disease risk and the slowing of HIV progression, due to an increase in TCD4+ lymphocytes and other components of the immune system.

The present study has some limitations, such as the zinc analysis. The number of replicates analyzed was probably not sufficient to presume a more certain level in the plasma. Inflammatory parameters, if analyzed together, could provide important information relative to zinc levels offered to patients and parameters to determine whether the disease is accelerating or not. Also, the number of participants included was lower than initially considered due to a lack of volunteers and a loss of data by the patients.

CONCLUSION

Zinc supplementation in biscuits showed a positive response, especially for TCD4+ lymphocytes couting and the incidence of opportunistic diseases in the analyzed period. The general improvement in health status reported by study participants shows that zinc supplementation can be quite promising. Supplementation seems to be a viable alternative for the population affected by HIV, and aims to innovate public policies to young and elderly, groups in which AIDS reaches an epidemic status.

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Recebido em: 2021

Aprovado em: 2021

Publicado em: 2021