



# No Relation Between Zinc Status and Inflammatory Biomarkers in Adolescent Judokas

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**Abstract:** This study aimed to assess the relation between zinc status and inflammation biomarkers in adolescent judokas. This cross-sectional study included 52 male adolescents, aged between 14 and 19 years, who were subdivided into two groups: judoka group (n = 25) and control group (n = 27). Zinc intake was monitored using 3-day food records and the NutWin software version 1.5. The plasma and erythrocyte zinc concentrations were determined by flame atomic absorption spectrophotometry. Analysis of cytokines (IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) was performed. The mean values of zinc concentration in the diet were found to be higher than those recommended (11.0  $\pm$  3.9 mg/day and 20.3  $\pm$  11.9 mg/day for control group and judokas, respectively) although there was no significant difference between the groups. The mean plasma concentrations of zinc were below the reference range (71.4  $\pm$  16.0  $\mu$ g/dL and 71.9  $\pm$  13.8  $\mu$ g/dL for control group and judokas, respectively), without a significant difference between the groups. The mean concentrations of zinc erythrocyte were within the reference range (41.2  $\pm$  8.6  $\mu$ g/gHb and 42.6  $\pm$  11.3  $\mu$ g/gHb for control group and judokas, respectively), without a significant difference between the groups. There was no significant difference in the inflammatory biomarkers between the judokas and controls. There was not a significant correlation between biochemical parameters of zinc and inflammation biomarkers in adolescent judokas. Regarding the data found in the study, it can be concluded that the athletes evaluated have low plasma zinc concentrations, normal erythrocyte values, and high dietary intake of zinc. Moreover, the study don't show a relationship between zinc parameters and inflammatory markers evaluated.

**Keywords:** Inflammation, judokas, nutritional status, zinc

## Introduction

Physical exercise promotes increased energy metabolism with synthesis of reactive oxygen species and inflammatory markers [1]. Furthermore, hormonal changes occur in period of adolescence, such as the increase of sexual steroids concentration, which contribute to exacerbate the oxidative stress and inflammation induced by exercise [2].

In this sense, some cytokines appear to alter the metabolism of minerals, such as zinc, but the mechanisms underlying this phenomenon are not yet clear [3, 4]. Zinc is an essential mineral that promotes stabilization of cell membranes and structural proteins and cell signaling. Moreover, zinc is a cofactor of more than 300 metalloenzymes such as carbonic anhydrase and lactate dehydrogenase, which are

involved in intermediary metabolism during exercise. Zinc also participates in catalytic activity of superoxide dismutase, which protects from oxidative damage caused by exercise [5-7].

Studies show changes in zinc homeostasis in athletes [8-10]. The systematic review and meta-analysis of Chu et al. [8], for example, indicated significant increase in serum zinc concentrations immediately after an aerobic exercise session, and they showed that changes in serum zinc are influenced by exercise intensity, the mode of exercise and the participants training status. Higher increase in serum zinc concentrations was observed after maximally exercise testing, running and in untrained individuals.

Muscle contractions performed during exercise, especially in impact, short duration, and high-intensity exercise

such as judo, cause disruption of muscle tissue, leading to the rapid release of zinc into the extracellular fluid, and as a result, an increase in plasma zinc. On the other hand, the subsequent reduction of this mineral's level in serum occurs due to its redistribution to the liver and erythrocytes, under the influence of circulating interleukins [11–13]. In this regard, interleukin  $1\beta$  (IL- $1\beta$ ), IL-6, and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) are the cytokines that show the most relevant changes in expression during exercise [3, 4, 11, 14].

Studies have revealed that cytokines IL- $1\beta$ , IL-6, and TNF- $\alpha$  stimulate expression of genes coding for metallothionein and the zinc transporter protein Zip-14 in plasma membrane; this change promotes the zinc influx into cells such as hepatocytes [15, 16]. Therefore, the increase in expression of these proteins results in this mineral's accumulation in specific tissues and a consequent reduction of its plasma concentrations. Thus, the inflammatory process seems to play an important role in zinc homeostasis in the body of individuals practicing intensive physical exercise [17].

Considering the scarcity of data on the metabolic behavior of zinc in anaerobic-exercise practitioners and the anti-inflammatory effect of this mineral, the aim of this study was to assess the relationship between zinc status and inflammation biomarkers in adolescent judokas.

## Methods

This was a cross-sectional study, with cases and controls, involving 52 male adolescents, aged between 14 and 19 years. This study involved only male athletes aiming to minimize the influence of specific female hormonal factors. The participants were subdivided into two groups: control ( $n = 27$ ) and athletes ( $n = 25$ ). The study participants were selected according to the following inclusion criteria: minimum training time equal to or greater than one year (judokas) or the absence of any physical activity (controls); no smoking; no diseases that can interfere with the nutritional status of zinc, e.g., diabetes mellitus and chronic renal failure; the absence of mineral supplements or vitamins in the diet or medications such as corticosteroids and penicillin, which can influence the testing for this mineral. The extreme weight judo athletes, with more than 100 kg, were excluded.

The determination of sample size ( $n = 25$ ) was based on the number of members of the Selection Piauiense Judo at the age of interest ( $n = 35$ ), accounting for approximately 70% of the study population.

The study's protocol was approved by the Ethics Committee of the Federal University of Piauí, with protocol number

62/09. The study participants or their legal guardians (when the participants were younger than 18 years) signed the Consent Form, and the study was conducted in accordance with the Declaration of Helsinki.

## Evaluation of Nutritional Status

To assess this status, we determined the body-mass index calculated as the participant's body weight divided by the square of the height. The classification of nutritional status was performed according to the recommendation of the World Health Organization [18]. The measurement of waist circumference was performed using a flexible, inelastic tape surrounding the natural waistline; the narrowest area between the chest and the hips was used as a reference value, as proposed by the World Health Organization [19]. The determination of body composition was performed using the bioelectrical impedance with a Biodynamics device model 310 Body Composition Analyzer (Biodynamics Corp., Shoreline, WA, 1995).

## Measurement of Zinc Intake

Food consumption was recorded using a 3-day food diary containing two alternate days during the week and one day on the weekend (Saturday or Sunday). At the time of submitting forms, guidelines were provided as to the correct way to write down the foods, such as to list the types of meals, preparation, portioning, portion sizes and times in which they were consumed. Upon receipt, the records were checked by researchers. The zinc content of the diet was calculated using the NutWin analysis software version 1.5 provided by the Federal University of Sao Paulo [20]. The Estimated Average Requirement (EAR) and Recommended Dietary Allowances (RDA) for zinc served as references values for suitable intake, being 8.5 mg/day (EAR) and 11 mg/day (RDA) for males aged between 14 and 18 years [21, 22].

## Assessment of Maximum Oxygen Consumption

Evaluation of maximum oxygen consumption ( $VO_{2max}$ ) was performed at baseline and served as a characterization tool for the participants (athletes and controls).  $VO_{2max}$  was determined using spirometry in the Exercise Physiology Laboratory of the NOVAFAPI Faculty, by a specialist using the ErgoPC Elite system (MicromedBiotecnologia LTDA., Brasília, Brazil, 2002).

## Assessment of Biochemical Parameters of Zinc

Fourteen-milliliter samples of venous blood were collected in the morning, between 7 and 9 a.m., after the participants had fasted for at least 12 h, and in case of judokas, at least 24 h without exercise. The collected blood was distributed in two distinct tubes: (1) a polypropylene tube containing 30% sodium citrate as an anticoagulant (10  $\mu$ L/mL blood) for zinc analysis (10 mL of blood) and (2) an EDTA tube for cytokine analysis (5 mL of blood).

Plasma was separated from whole blood using centrifugation (CIENITEC<sup>®</sup> 4 K15, São Paulo, Brazil) at  $1831 \times g$  for 15 min at 4 °C. Subsequently, plasma was extracted with an automatic pipette, placed in the previously demineralized polypropylene microtubes, and stored at -20 °C. To isolate erythrocytes for the measurement of zinc concentration, the methods proposed by Whitehouse et al. [23] were used. The red blood cell mass was washed with 5 mL of isotonic saline (0.9% NaCl), was slowly homogenized by inversion, and was centrifuged at  $1831 \times g$  for 10 min. The supernatant was then aspirated and discarded. The procedure described was performed three times to remove any contaminants from erythrocytes (i.e., platelets and leukocytes) [22].

Zinc analysis in plasma and erythrocytes was conducted using flame atomic absorption spectrophotometry, according to the method described by Rodriguez et al. [24]. Tritisol<sup>®</sup> (MERCK) prepared by dilution with MilliQ<sup>®</sup> water at concentrations of 0.1, 0.2, 0.3, 0.5, and 1.0  $\mu$ g/mL served as a standard.

## Plasma concentrations of IL-1 $\beta$ , IL-6, and TNF- $\alpha$

Analysis of cytokines was performed by means of a commercial kit according to the manufacturer's instructions (Lincoplex Cytokine analytes, Linco Research, Missouri, USA), on the basis of the ELISA principle. The limits of detection for IL-1 $\beta$ , IL-6, and TNF- $\alpha$  were from 0.4 to 0.7 pg/mL, 0.3 to 0.7 pg/ml, and 0.1 pg/ml, respectively.

## Statistical analysis

The data were analyzed using the software packages S-PLUS v.3.2 Release, Minitab for Windows Release 11.0, and SPSS (for Windows<sup>®</sup> version 9.0). The Kolmogorov-Smirnov test was conducted to verify the normality of the data. To compare outcome measures between the two groups of subjects, Student's *t* test or Mann-Whitney *U* test was performed for parametric and nonparametric data, respectively. Additionally, Pearson's or Spearman correlation test was used considering parametric or

non-parametric variables, respectively. A difference was considered statistically significant when the *p* value was <0.05, with a 95% confidence interval.

## Results

The mean values and standard deviations for the anthropometric parameters used to assess the nutritional status of judokas and control subjects are shown in Table I. There were significant differences in the body weight, body-mass index, body fat, lean body mass, and fat mass (*p* < 0.05).

Mean values and standard deviations for VO<sub>2max</sub> were 24.0  $\pm$  7.1 mL/(kg·min) for the control group and 42.4  $\pm$  6.5 mL/(kg·min) for judokas. This difference was significant (Student's *t* test, *p* < 0.001). VO<sub>2max</sub> was higher in athletes, which shows that these adolescents had greater physical fitness and endurance than the control group did.

Table II shows the means and standard deviation of energy, macronutrients, and zinc present in the diet ingested by control subjects and judokas. The mean values of dietary zinc were found to be higher than those recommended. There was a significant difference in the

**Table I.** Means and standard deviation of body weight, height, body mass index, body fat, lean body mass and fat mass in the control group and judokas.

Parameters	Control (n = 27)	Judokas (n = 24)	p
	Mean $\pm$ SD	Mean $\pm$ SD	
Weight (kg)	58.0 $\pm$ 9.0	66.2 $\pm$ 8.9	0.002
Height (m)	1.68 $\pm$ 0.08	1.72 $\pm$ 0.07	0.162
BMI (kg/m <sup>2</sup> )	20.4 $\pm$ 2.6	22.5 $\pm$ 2.0	0.003
BF (%)	19.4 $\pm$ 6.4	11.7 $\pm$ 3.9	<0.001
LBM (kg)	49.8 $\pm$ 22.2	58.3 $\pm$ 7.4	0.080
FM (kg)	12.3 $\pm$ 7.7	7.8 $\pm$ 3.3	0.012

Values significantly different between the judokas and control groups using Student's *t*-test (*p* < 0.05). SD: standard deviation; BMI: body mass index; BF: body fat; LBM: lean body mass; FM: fat mass.

**Table II.** Means and standard deviation of energy, macronutrients, and zinc present in the diet ingested by control subjects and judokas.

Parameters	Control (n = 25)	Judokas (n = 24)	p
	Mean $\pm$ SD	Mean $\pm$ SD	
Energy (kcal)	1950.0 $\pm$ 656.3	3261.5 $\pm$ 2013.3	0.005
Carbohydrate (%)	52.6 $\pm$ 6.4	51.0 $\pm$ 7.2	0.431
Protein (%)	22.7 $\pm$ 5.3	22.0 $\pm$ 6.2	0.673
Lipid (%)	24.7 $\pm$ 3.5	27.0 $\pm$ 3.9	0.039
Dietary Zinc (mg/day)	11.0 $\pm$ 3.9	20.3 $\pm$ 11.9	< 0.001
Dietary Zinc (mcg/kcal/day)	5.8 $\pm$ 1.6	6.4 $\pm$ 0.9	0.147

Values significantly different between the judokas and control groups using Student's *t*-test or Mann-Whitney *U* test (*p* < 0.05). Reference values: Protein: 10-35%; Lipid: 20-35%; Carbohydrates: 45-65% (IOM, 2005). Dietary Zinc: EAR = 8.5 mg/day, RDA = 11 mg/day [22]. SD: standard deviation.

**Table III.** Means and standard deviation of biochemical parameters of zinc and plasma inflammatory biomarkers in the control group and judokas.

Parameters	Control (n = 23)	Judokas (n = 24)	p
	Mean ± SD	Mean ± SD	
Plasma Zinc (µg/dL)	71.4 ± 16.0	71.9 ± 13.8	0.914
Plasma Zinc (µg/dL/Kg LBM)	1.61 ± 0.69	1.25 ± 0.30	0.030
Plasma Zinc (µg/dL/Kg FM)	7.4 ± 4.0	10.8 ± 5.5	0.018
Erythrocyte Zinc (µg Zn/gHb)	41.2 ± 8.6	42.6 ± 11.3	0.632
IL-1β (pg/mL)	1.15 ± 0.80	1.37 ± 0.42	0.347
IL-6 (pg/mL)	3.25 ± 0.97	2.25 ± 0.50	0.156
TNF-α (pg/mL)	11.24 ± 3.02	10.11 ± 3.01	0.226

Values significantly different between the judokas and control groups using Student's t-test ( $p > 0.05$ ). Reference values: Plasma Zinc: 75-110 µg/dL [25]; Erythrocyte Zinc: 40-44 µg/gHb [26]. SD: standard deviation. BF: body fat; LBM: lean body mass; FM: fat mass; IL-1β: interleucina 1β; IL-6: interleucina 6; TNF-α: fator de necrose tumoral α.

consumption of this mineral ( $p < 0.05$ ) between the groups. However, there was not statistical difference for dietary zinc per kilocalories per day ( $p > 0.05$ ) between the groups.

Mean values and standard deviation of biochemical parameters of zinc and plasma values of IL-1β, IL-6, and TNF-α for control subjects and judokas are shown in Table III. There was no significant difference in plasma and erythrocytic zinc levels between the groups ( $p > 0.05$ ). However, there was statistical difference for plasma zinc per kilograms of lean body mass per day and for plasma zinc per kilograms of fat mass per day ( $p < 0.05$ ) between the groups. There was no significant difference in the inflammatory biomarkers between judokas and the control group ( $p > 0.05$ ).

Table IV shows the linear simple correlation between zinc status and plasma inflammatory biomarkers in control group and judokas. There was not a significant correlation between biochemical parameters of zinc and inflammation biomarkers in adolescent judokas ( $p > 0.05$ ).

## Discussion

In this study, we determined certain biomarkers of zinc status and we analyzed their relationship to plasma

concentrations of proinflammatory cytokines in adolescent judokas. The judokas showed the mean zinc intake above the EAR and RDA values, with statistically significant differences between both athletes and control group ( $p < 0.05$ ). The consumption of zinc by the participants of this study can be explained by the usual protein intake, especially red meat and other animal foods: known dietary sources of zinc that are a part of eating habits in these groups [27-29].

It is noteworthy that the mean zinc intake in mg/kcal/day was not statistically different between the groups. This result evidences that the higher caloric consumption may have contribute to for the higher zinc intake of judokas.

The dietary intake of zinc did not influence the plasma levels of this nutrient in the athletes, given that the judokas had high average values of dietary zinc and a reduced concentration of zinc in plasma, without significant difference between the groups in this study ( $p > 0.05$ ). However, the findings of Casimiro-Lopes et al. [30], who also evaluated the plasma zinc concentrations in judo athletes 24 hours after completion of training, showed adequate values of this biomarker.

The reduced plasma levels of zinc in judokas may be due to increases in plasma volume induced by exercise or due to changes in the distribution of zinc in the body of physically active people, characterized by increased levels of this mineral in specific tissues, such as liver [11, 12, 31].

In addition, it should be mentioned that the assessment of plasma zinc in this study was performed 24 hours after exercise. In this regard, the literature shows high levels of zinc in the plasma immediately after high-intensity exercise, which may be due to the disruption of muscle tissue, leading to the rapid release of zinc into the extracellular fluid [8, 11]. However, studies evaluating the levels of zinc in plasma or serum, a day or a few weeks after the exercise, showed reduced concentrations of zinc, corroborating the findings of our study [12, 32, 33].

On this point, researches show an increase in plasma volume of athletes 24-hours after exercise, and it could be due to an increase in plasma protein mass, that creates an osmotic gradient for water movement into the vascular space; to a decrease in central venous pressure, that would facilitate greater flux of fluid from the lymphatic system or interstitial

**Table IV.** Analysis of linear simple correlation between plasma and erythrocyte zinc and plasma inflammatory biomarkers in control group and judokas.

Parameters	Plasma Zinc				Erythrocyte Zinc			
	Control		Judokas		Control		Judokas	
	r	p	r	p	r	p	r	p
IL-1β	-0.098	0.750	0.205	0.523	0.313	0.257	0.358	0.254
IL-6	0.414	0.586	0.919	0.258	0.916	0.029*	0.483	0.679
TNF-α	0.455	0.058	0.285	0.211	0.045	0.858	-0.029	0.899

\*Pearson's linear correlation ( $p < 0.05$ ).

space; and/or an increase in renal fluid retention [34–37]. In this way, this hypervolemia could contribute to the reduced plasma concentrations of zinc in judokas in our study.

It is worth mentioning that body composition may influence plasma concentration of zinc. In our study, the judokas showed reduced values of plasma zinc in  $\mu\text{g}/\text{dL}/\text{Kg}$  of lean body mass, when compared with control group. This result can be explained by the higher lean body mass in judokas that is associated with higher plasma volume. The increase in plasma volume promotes hemodilution of zinc, reducing its plasma values. On the other hand, the levels of plasma zinc in  $\mu\text{g}/\text{dL}/\text{kg}$  of body fat were elevated in judokas, in relation to control group because the body fat is associated with lower plasma volume.

Regarding the determination of average concentrations of zinc in red blood cells, this assay showed no statistically significant difference between the groups ( $p > 0.05$ ). These results are consistent with the study by Mundie and Hare [38], which revealed no difference in erythrocytic zinc concentrations 24 hours after a session of anaerobic exercise in athletes compared to the control group.

Scarcity and discrepancies in the results of studies on erythrocytic zinc in athletes engaged in strenuous activities limit the broader discussion of the topic. In this sense, the literature shows a relation between zinc concentrations in erythrocytes and the mode and intensity of exercise. Anaerobic activity, like judo, seems to result in a high metabolic and nutritional demand, in line with the usually observed increase in the activity of the enzymes superoxide dismutase and carbonic anhydrase, both zinc-dependent, and even a loss of this mineral with sweat [39, 40]. These factors may have contributed to the finding that the zinc values in judokas' erythrocytes did not show a significant difference from those in controls, although they had high zinc levels in the diet.

The mean values of plasma concentrations of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  showed no significant differences between the groups ( $p > 0.05$ ). These results are similar to those reported by Oliveira, Procida, and Borges-Silva [41], who also analyzed the plasma concentrations of IL-6 and TNF- $\alpha$  in judo athletes and found no statistically significant differences between the athletes and controls.

The literature shows that there is substantial variability in the results of studies involving the analysis of cytokines. According to Pedersen [42], the explanation for this variation is the absence of homeostatic control of these substances because their synthesis is influenced by the type, duration, and intensity of exercise. This reasoning may help to explain the absence of statistically significant differences in IL-1 $\beta$ , IL-6, and TNF- $\alpha$  levels in this study.

In light of a better understanding of the results, we conducted an analysis of correlation between zinc status parameters and the evaluated inflammatory biomarkers,

and it was not observed significant result. However, Liuzzi et al. [43] showed the influence of IL-6 on the manifestation of hypozincemia associated with an acute inflammatory response.

Increase in IL-6 concentration appears to contribute to changes in zinc metabolic patterns through redistribution of plasma zinc to the liver, where it remains attached to metalloproteins, such as metallothionein. Furthermore, it has been demonstrated that IL-6 also regulates the expression of the protein Zip14 in hepatic tissue; this mechanism may facilitate zinc compartmentalization in that organ and thereby reduce its concentration in plasma [43]. It is emphasized that factors such as accelerated growth in adolescence and metabolic disorders resulting from exercise are also important for changes in zinc metabolism [11, 44].

Therefore, it appears that further research is needed on this topic for a better understanding of the metabolic behavior of zinc in the metabolic changes induced by exercise, particularly in relation to the increased plasma concentrations of inflammatory biomarkers.

This study has certain limitations. The assessment of dietary intake is susceptible to random and systematic errors, and can be affected by the number of days. In order to minimize, the data of zinc obtained were subsequently adjusted on the basis of energy intake and intra-individual variation. Another limitation is the reduced number of participants of this study.

Judokas evaluated in this study eat diets with high zinc content. Biochemical parameters of this mineral in the study participants show adequate zinc concentrations in erythrocytes and reduced levels in plasma. Moreover, the study don't show a relationship between zinc parameters and inflammatory markers evaluated.

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#### **Conflict of Interest**

The authors declare that there are no conflicts of interest.

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