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Clinical studies

Association of reduced zinc status with poor glycemic control in individuals with type 2 diabetes mellitus

Verônica da Silva Bandeira[a], Liliane Viana Pires[b,*], Leila Leiko Hashimoto[a], Luciane Luca de Alencar[a], Kaluce Gonçalves Sousa Almondes[a], Simão Augusto Lottenberg[c], Silvia Maria Franciscato Cozzolino[a]

[a] Nutrition-Minerals Laboratory, Department of Food and Experimental Nutrition, Faculty of Pharmaceutical Sciences, University of São Paulo, Av. Prof. Lineu Prestes, 580–Bloco 14, Butantã, 05508900, SP, Brazil
[b] Department of Nutrition, Federal University of Sergipe, Avenida Marechal Rondon, S/n – Jardim Rosa Elze, 49100000, São Cristovão, Sergipe, Brazil
[c] Clinics Hospital of the Faculty of Medicine of the University of São Paulo, Endocrinology and Metabolism Service, Av. Dr. Enéas Carvalho de Aguiar, 255, 05403900, São Paulo, Brazil

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ABSTRACT

This study evaluated the relationship between the zinc-related nutritional status and glycemic and insulinemic markers in individuals with type 2 diabetes mellitus (T2DM). A total of 82 individuals with T2DM aged between 29 and 59 years were evaluated. The concentration of zinc in the plasma, erythrocytes, and urine was determined by the flame atomic absorption spectrometry method. Dietary intake was assessed using a 3-day 24-h recall. In addition, concentrations of serum glucose, glycated hemoglobin percentage, total cholesterol and fractions, triglycerides, and serum insulin were determined. The insulin resistance index (HOMA-IR) and β-cell function (HOMA- β) were calculated. The markers of zinc status (plasma: 83.3 ± 11.9 μg/dL, erythrocytes: 30.1 ± 4.6 μg/g Hb, urine: 899.1 ± 622.4 μg Zn/24 h, and dietary: 9.9 ± 0.8 mg/day) were classified in tertiles and compared to insulinemic and glycemic markers. The results showed that lower zinc concentrations in plasma and erythrocytes, as well as its high urinary excretion, were associated with higher percentages of glycated hemoglobin, reflecting a worse glycemic control in individuals with T2DM ($p < 0.05$). Furthermore, there was a significant inverse correlation between plasma zinc levels and glycated hemoglobin percentage ($r = -0.325$, $p = 0.003$), and a positive correlation between urinary zinc excretion and glycemia ($r = 0.269$, $p = 0.016$), glycated hemoglobin percentage ($r = 0.318$, $p = 0.004$) and HOMA-IR ($r = 0.289$, $p = 0.009$). According to our study results, conclude that T2DM individuals with reduced zinc status exhibited poor glycemic control.

1. Introduction

Zinc dyshomeostasis is a common phenomenon that is observed in individuals with diabetes over the years [1–5], mainly due to the deficiency of this mineral in the plasma and hyperzincuria [6–8]. These disturbances in zinc metabolism have also been associated with poor metabolic control of diabetes [5].

The established relationship between zinc and glucose metabolism is attributed to the role of the nutrient in the crystallization and signaling of insulin. Physiologically, zinc is abundant in the pancreas, and is mainly concentrated in the insulin secretory vesicles of the beta cells, since it forms the structure of this hormone, and serves to stabilize and minimize the susceptibility of insulin to oxidative damage [7,9]. In addition, zinc has been associated with insulin sensitivity through activation of the phosphoinositol-3-kinase/protein kinase B cascade. This was observed in rat adipocytes and fibroblasts [10], in rat hepatocytes [11], and in human lung cells [12]. The activation of this cascade contributes to the regulation of glucose transport, glycogen synthesis, gluconeogenesis, lipogenesis, and protein synthesis.

Studies have linked low plasma and serum zinc concentrations to reduced insulin sensitivity, and subsequent hyperglycemia. Moreover, an improvement in glycemic parameters has been demonstrated following zinc supplementation [8,13,14]. In a *meta*-analysis of various zinc supplementation studies, a modest reduction in the glucose values and possible decrease in the glycated hemoglobin percentage in individuals with type 2 diabetes mellitus (T2DM) were highlighted [8].

Assessing the relationship between the zinc-related nutritional status and the insulinemic and/or glycemic parameters will further

* Corresponding author.
E-mail addresses: lvpires@usp.br, lvianapires@gmail.com (L.V. Pires).

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justify the role of this mineral in glucose homeostasis. This study evaluated the dietary intake and concentrations of zinc in the plasma, erythrocytes, and urine of individuals with T2DM, and their relationship with glycemic control parameters.

2. Material and methods

2.1. Study population

Eighty-two male and female volunteers aged 29–59 years, who underwent clinical follow-up at the Endocrinology and Metabology Service of the Hospital das Clínicas of the Medical School of the University of Sao Paulo, Sao Paulo, Brazil, were selected according to the following inclusion criteria: presence of T2DM but not on insulin medication, nonsmokers, occasional drinkers, and the absence of other chronic noncommunicable diseases, which could interfere with the zinc status.

This study was conducted according to the guidelines of the Declaration of Helsinki. Approval was obtained from the Research Ethics Committee of the Faculty of Pharmaceutical Sciences of the University of São Paulo (protocol number: 414.203). A free and informed written consent was obtained from all study participants.

2.2. Anthropometric assessment

Anthropometric measurements of weight (kg) and height (cm) were performed according to Frisancho's [15] methodology. Then, body mass index (BMI) was calculated and classified as proposed by the World Health Organization [16]. In order to evaluate fat percentage, the Biospace body composition analyzer (In Body 720 model) was used and the results were based on the cut-off points recommended by Pollock and Wilmore [17]. The measures of waist circumference (WC) were classified according to the reference values proposed by the World Health Organization [16].

2.3. Evaluation of food intake of zinc

A 3-day (non-consecutive) 24-h dietary recall was used to assess dietary intake. The analysis of dietary intake of the participants was performed using the NutWin Software, version 2.5. The adequacy of zinc intake was assessed by comparing the dietary zinc values with the Estimated Mean Requirement proposed by the Institute of Medicine [18]. Energy adjustment of the zinc values was also performed [19].

2.4. Obtaining samples

2.4.1. Blood

Blood samples (20 mL) were collected from 10 to 12 h-fasted participants and aliquoted into 3 tubes: the first tube free of trace elements (for zinc analysis) contained sodium heparin, the second contained EDTA (for determination of glycated hemoglobin), and the third tube did not contain an anticoagulant (for analysis of insulin, glucose, triglycerides, total cholesterol, and fractions). To obtain plasma and serum, blood samples were centrifuged at 3.000 rpm for 15 min at 4 °C. The erythrocytes were then washed three times with 3 mL of 0.9% NaCl solution, slowly homogenized by inversion, centrifuged at 10.000 rpm for 10 min, at 4 °C, and the supernatant discarded. Whole blood and serum samples were stored in sterile microtubes, whilst plasma and erythrocyte mass were stored in demineralised microtubes. All samples were stored at −80 °C.

2.4.2. Urine

Participants were instructed to collect their urine for a 24-h period in demineralised flasks.

2.5. Determination of zinc concentration in plasma, erythrocytes, and urine

The determination of plasma [20,21], erythrocyte [22], and urine [23] zinc concentration was performed in duplicate by flame atomic absorption spectrometry method (HITACHI® model Z-5000), calibrated to wavelength 213.9 nm, slit 0.4 nm, oxidizing flame with air mixture (15.0 L/min): acetylene (2.0 L/min). A standard zinc curve using Tritizol® (MERCK®) was prepared following concentrations: 0.01; 0.02; 0.03; 0.05; 0.1; 0.3; 0.5 µg/mL, diluted in nanopure water. For the plasma zinc analysis, 3% glycerol solution was added to the calibration curve. The samples plasma, erythrocytes, and urine were diluted in nanopure water in proportion of 1:5; 1:40 and 1:4, respectively. The hemoglobin concentration in the erythrocytes was determined and the results of zinc in erythrocytes were expressed µg Zn/g Hb. The concentrations of zinc in plasma and urine were expressed in µg/dL and µg Zn/24 h, respectively. The control used was SERONORM® certified reference material (serum, whole blood, and urine).

2.6. Glycemic and lipid parameters

Serum glucose concentration (mg/dL) and glycated hemoglobin (%) were assessed using commercial kits (Labtest, Lagoa Santa, Minas Gerais, Brazil). The concentrations of total plasma cholesterol, HDL-cholesterol, and triglycerides (TG) were determined using commercial enzymatic methods (Labtest, Lagoa Santa, Minas Gerais, Brazil). HDL cholesterol level was determined after the precipitation of LDL and TG fractions. The LDL fraction was calculated using the Friedwald, Levy and Fredrickson [24] equation.

2.7. Determination of serum insulin and Homeostasis Model Assessment calculations (HOMA)

The serum insulin concentration was determined based on the sandwich-type immunoassay method, using the principle of chemiluminescence (Advia Centaur Siemens®). The HOMA-IR and HOMA β values [25] were used to evaluate the insulin resistance index and β-cell function, respectively.

2.8. Statistical evaluation

Statistical analyses were performed using the Statistical Package for Social Sciences, version 14.0 (SPSS Chicago IL USA). The results were presented as average, standard deviation, absolute and relative frequencies. The Kolmogorov-Smirnov test was performed to normality analysis.

Pearson's linear correlation coefficient was used to verify the correlations between the parameters of the zinc status and the insulinemic and glycemic parameters.

The ANOVA test and Tukey's test were also employed in the study. Biomarkers of zinc status were classified into tertiles, and compared with the insulinemic and glycemic markers.

In relation to the zinc intake, the energy provided by the diet was adjusted by the residual method proposed by Willet (1998), using simple linear regression.

A fixed confidence level of 95% ($p < 0.05$) was adopted and considered significant.

3. Results

Table 1 shows the clinical, glycemic and zinc status characteristics of the participants.

We observed significant negative correlation between plasma zinc concentration and percentage of glycated hemoglobin ($r = -0.325$, $p = 0.003$), and positive correlations between concentrations 24-h urinary zinc excretion and glycemia ($r = 0.269$, $p = 0.016$), percentage of glycated hemoglobin ($r = 0.318$, $p = 0.004$) and HOMA–IR

Table 1
Clinical, biochemical and zinc status characteristics of individuals with T2DM.

Variables	T2DM (n = 82)
Gender	
Male, n (%)[a]	51(62)
Age (years)	50.7 ± 6.9
Disease diagnosis time (years)	7.3 ± 6.8
Family history of diabetes, n (%)[a]	69 (84.1)
Hypertension, n (%)[a]	43 (52.4)
Weight (kg)	81.4 ± 19.4
Height (cm)	166.0 ± 10.0
BMI (kg/(m)^2)	29.1 ± 5.3
Waist circumference (cm)	97.5 ± 12.6
Body fat (%)	35.0 ± 9.2
Serum glycemia (mg/dL)	150.3 ± 53.6
Glycated hemoglobin (%)	8.1 ± 1.2
Serum insulin (μUI/mL)	17.4 ± 10.6
HOMA-IR	6.5 ± 4.5
HOMA-β	42.3 ± 30.7
Total cholesterol (mg/dL)	188.5 ± 62.5
HDL-c (mg/dL)	44.5 ± 11.7
Triglycerides (mg/dL)	161.6 ± 125.3
LDL-c (mg/dL)	108.6 ± 44.4
Plasma Zn (μg/dL)	83.3 ± 11.9
Urinary Zn (μg Zn/24 h)[b]	899.1 ± 622.4
Erythrocyte Zn (μg/g Hb)	30.1 ± 4.6
Zn dietary intake (mg/day)	9.9 ± 0.8

Data presented as mean (standard deviation).
[a] Data presented as *n* (%).
[b] n = 80.

(r = 0.289, p = 0.009) (Fig. 1). We did not observe significant associations between the other glycemic control variables and markers of the nutritional status of zinc.

The results of the glycemic and insulinemic markers of individuals with T2DM were distributed according to the tertile of the biochemical variables of the zinc status. Results that corroborate the correlations are shown in Table 2.

4. Discussion

Previous studies have linked zinc to glycemic control in individuals with T2DM [4,8,26]. In this study, we found significant associations between short and long term markers of zinc status and glycemic and insulinemic markers in individuals with T2DM.

Our findings indicated that the plasma zinc levels for all individuals with T2DM in our study cohort were normal, a result similar to that found in individuals with T2DM also living in Brazil [27]. However, most studies in other countries have demonstrated low zinc concentrations in the plasma and/or serum of individuals with T2DM [28,29].

Zinc status is commonly assessed by its plasma or serum concentrations. However, this assessment reflects the status in a short period of time and is dependent on the zinc intake. Foods containing animal proteins are great sources of zinc. The quality and quantity of the protein present in the diet is associated with the absorption of this mineral [30–33].

It is recommended that three or more biomarkers be evaluated to assess the individual's nutritional zinc status [32], since no definite consensus regarding the most appropriate biomarker has yet been

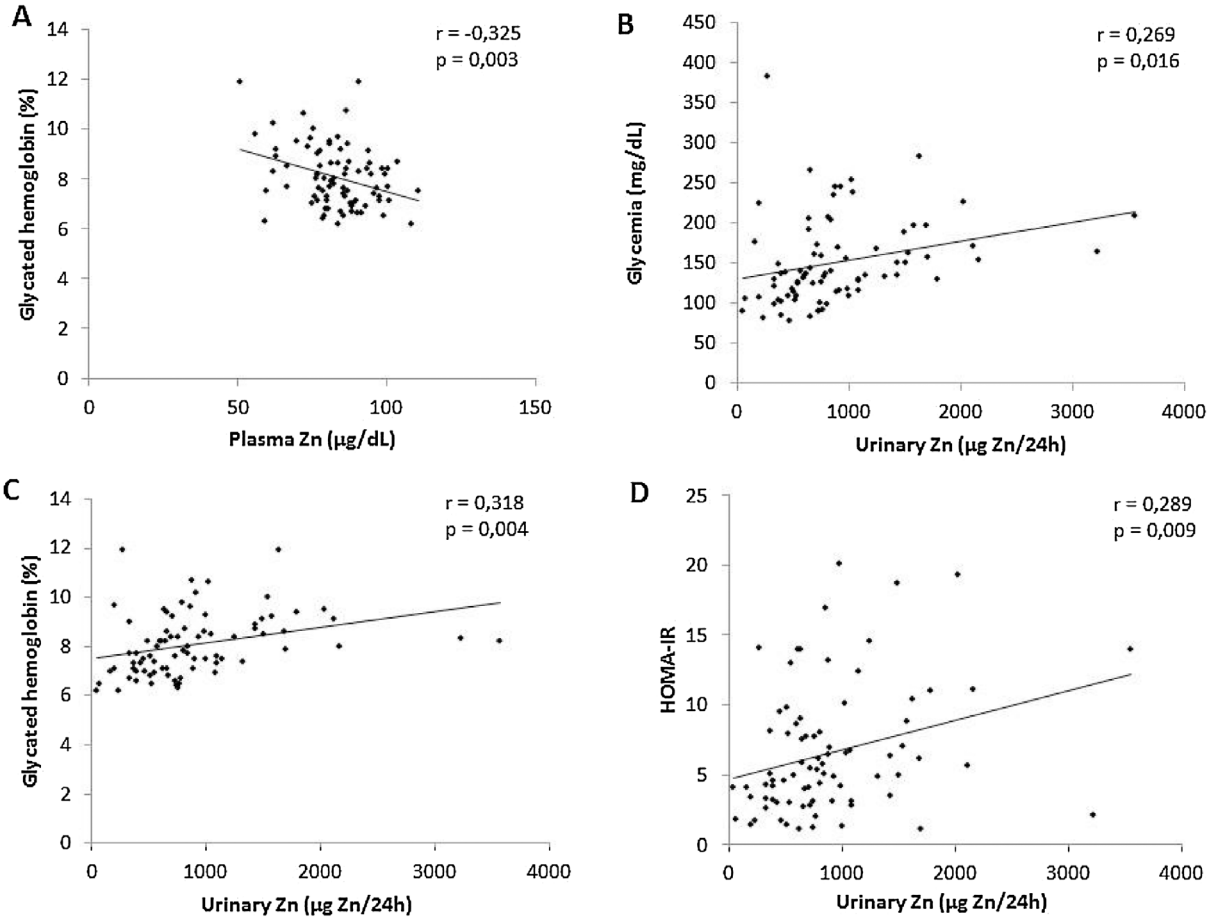

Fig. 1. Correlations (r) between plasma zinc concentrations and percentage of glycated hemoglobin (A), and 24-h urinary zinc excretion and serum glucose (B), percentage of glycated hemoglobin (C) and HOMA-IR (D).

Table 2
Zinc status in plasma, erythrocytes, urine, and dietary zinc in relation to the insulinemic and glycemic markers of individuals with T2DM.

Variables	Tertile I	Tertile II	Tertile III	p^*
Plasma Zn (μg/dL)[1]	n = 27	n = 28	n = 27	
Glycemia (mg/dL)	156.56 ± 63.75	147.75 ± 48.30	146.60 ± 50.23	0.763
Serum insulin (μUI/mL)	17.44 ± 10.37	18.19 ± 10.63	16.63 ± 11.18	0.865
Glycated hemoglobin (%)	8.56 ± 1.32[a]	7.98 ± 1.13[ab]	7.68 ± 1.15[b]	0.028
HOMA-β	40.68 ± 29.40	45.16 ± 32.36	40.91 ± 31.02	0.833
HOMA-IR	6.86 ± 4.90	6.58 ± 4.42	6.04 ± 4.41	0.800
Erythrocyte Zn (μg/g Hb)[2]	n = 27	n = 28	n = 27	
Glycemia (mg/dL)	144.52 ± 46.74	156.82 ± 61.40	149.22 ± 53.75	0.699
Serum insulin (μUI/mL)	16.24 ± 11.08	16.13 ± 8.12	19.98 ± 12.25	0.318
Glycated hemoglobin (%)	8.06 ± 1.18[ab]	8.55 ± 1.32[a]	7.60 ± 1.06[b]	0.017
HOMA-β	38.81 ± 29.52	37.80 ± 25.30	50.42 ± 35.89	0.243
HOMA-IR	5.95 ± 4.35	6.16 ± 3.52	7.38 ± 5.58	0.463
Urinary Zn (μg Zn/24 h)[3]	n = 26	n = 27	n = 27	
Glycemia (mg/dL)	129.81 ± 59.88[a]	150.59 ± 50.59[ab]	169.96 ± 46.51[b]	0.025
Serum insulin (μUI/mL)	16.65 ± 10.74	16.89 ± 8.19	19.60 ± 12.52	0.532
Glycated hemoglobin (%)	7.50 ± 1.21[a]	8.08 ± 1.25[ab]	8.64 ± 1.08[b]	0.003
HOMA-β	48.93 ± 37.40	40.15 ± 23.90	40.27 ± 29.75	0.497
HOMA-IR	5.12 ± 3.48[a]	6.43 ± 4.05[ab]	8.21 ± 5.44[b]	0.042
Dietary Zn (mg/day)[4]	n = 25	n = 30	n = 27	
Glycemia (mg/dL)	149.12 ± 54.48	139.73 ± 56.24	163.04 ± 50.05	0.267
Serum insulin (μUI/mL)	17.30 ± 11.23	17.14 ± 10.69	17.87 ± 10.35	0.966
Glycated hemoglobin (%)	8.10 ± 1.43	8.00 ± 1.28	8.14 ± 1.03	0.914
HOMA-β	42.13 ± 30.53	44.85 ± 32.42	39.58 ± 29.67	0.814
HOMA-IR	6.47 ± 4.79	5.87 ± 4.17	7.20 ± 4.75	0.548

*p-values for one-way ANOVA. Values considered significant with $p < 0.05$. Different letters in the same line (a, b) indicate a significant difference between the means by Tukey's test ($p < 0.05$).

[1] Plasma Zn: Tertile I (< 79.07 μg/dL); Tertile II (79.07–87.81 μg/dL); Tertile III (> 87.81 μg/dL).

[2] Erythrocyte Zn: Tertile I (< 28.16 μg/g Hb); Tertile II (28.16–31.04 μg/g Hb); Tertile III (> 31.04 μg/g Hb).

[3] Urinary Zn: Tertile I (< 610.61 μg Zn/24 h); Tertile II (610.61–932.37 μg Zn/24 h); Tertile III (> 932.37 μg Zn/24 h).

[4] Dietary Zn: Tertile I (< 9.5 mg/day); Tertile II (9.5–10.16 mg/day); Tertile III (> 10.16 mg/day).

established [34]. This explains our evaluation of the concentration of zinc in plasma, erythrocytes, urine, and diet. Studies show that zinc deficiency can worsen glycemic levels [8,29,35]. Thus, it was observed that patients with lower concentrations of zinc in the plasma had worse glycemic control, as evidenced by percentage of glycated hemoglobin.

According to the ADA [36], a reduction in the percentage of glycated hemoglobin decreases the risk of microvascular complications of diabetes. However, the establishment of a therapy around 8% of glycated hemoglobin is due to the presence of factors that preclude better glycemic control, such as history of severe hypoglycemia, limited life expectancy, macro or microvascular complications, and high glycemic variability. In this study, the mean percentage of glycated hemoglobin found in individuals was 1% above the therapeutic target proposed for this population.

In vivo studies have evaluated the role of zinc in the secretory mechanisms of insulin. In adipocytes, it was observed that treatment with zinc increased glucose transport thereby, acting as a potentiator of this process, possibly via the insulin-signaling pathway [10].

In agreement with this, a study has demonstrated that individuals with a good glycemic control have better concentrations of zinc compared to those with worse glycemic control [3]. Since the discovery of the zinc transporter 8 (ZnT8), by Chimienti et al. [37], studies have tried to ascertain the exact mechanism of this transporter. Currently, it is known for its specificity for pancreatic beta cells, and it functions to transport zinc from the cytoplasm into intracellular vesicles. It is therefore an important component in the storage and secretion of insulin and glucose homeostasis.

Individuals with diabetes have metabolic disorders, and the erythrocyte zinc concentration is more accurate at assessing the nutritional status of these patients [38]. It was observed in this study that patients with lower concentrations of zinc in erythrocytes had worse percentage of glycated hemoglobin, compared to those with better zinc status. The elevated excretion of zinc in the urine suggests that it may be due to persistent hyperglycemia. High glycaemia can affect the renal system, and studies have shown that individuals with diabetes have hyperzincuria [39–41].

Quilliot et al. [42] evaluated individuals with T2DM diagnosed with chronic pancreatitis, one of the consequences of hyperglycemia, and noted an increase in the urinary zinc excretion in this population. In this study, the highest concentrations of glucose and percentage of glycated hemoglobin were observed in individuals with greater amounts of zinc in the urine.

A positive correlation was observed between urinary zinc excretion and the HOMA-IR index. It has been demonstrated that the higher the concentration of zinc in the urine, the greater the resistance to insulin [9,43].

Furthermore, this relationship was verified because the individuals with lower urinary zinc excretion (tertile I) presented lower values for insulin resistance compared to those with higher urinary zinc excretion (tertile III). A study with obese women found that, after supplementation of zinc, the HOMA-IR index values reduced, which strongly indicates a role of zinc in insulin resistance [44]. However, Kim and Lee [45] also observed in obese women that supplementation with 30 mg Zn/day for 8 weeks did not show significant results between urinary zinc excretion and insulin resistance.

Thus, implementing strategies that seek to improve zinc nutritional status in individuals with T2DM may favor glycemic control in order to minimize the complications of this disease.

5. Conclusion

The analysis zinc status in individuals with T2DM showed that lower zinc concentrations in plasma and erythrocytes, as well as its high urinary excretion, were associated with higher percentages of glycated hemoglobin, reflecting a worse glycemic control, thereby, evidencing the role of zinc in glucose metabolism. The results of this study highlight the importance of adjusting the amount of dietary zinc consumed by individuals with T2DM to optimize the zinc status with consequent

promotion of diabetes control by recognizing the relationship between this mineral and glucose metabolism.

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Authorship

The authors contributed as follows: Verônica da Silva Bandeira, Liliane Viana Pires and Silvia Maria Franciscato Cozzolino designed the study and participated in the data analyses, interpretation of the results, writing and critical review of the manuscript; and Leila Leiko Hashimoto, Luciane Luca de Alencar, Kaluce Gonçalves Sousa Almondes and Simão Augusto Lottenberg analyzed, interpreted the data and critical review of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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