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Comparative absorption of zinc picolinate, zinc citrate and zinc gluconate in humans*

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Abstract

The comparative absorption of zinc after oral administration of three different complexed forms was studied in 15 healthy human volunteers in a double-blind four-period crossover trial. The individuals were randomly divided into four groups. Each group rotated for four week periods through a random sequence of oral supplementation including: zinc picolinate, zinc citrate, and zinc gluconate (equivalent to 50 mg elemental zinc per day) and placebo. Zinc was measured in hair, urine, erythrocyte and serum before and after each period. At the end of four weeks hair, urine and erythrocyte zinc levels rose significantly ($p < 0.005$, $p < 0.001$, and $p < 0.001$) during zinc picolinate administration. There was no significant change in any of these parameters from zinc gluconate, zinc citrate or placebo administration. There was a small, insignificant rise in serum zinc during zinc picolinate, zinc citrate and placebo supplementation. The results of this study suggest that zinc absorption in humans can be improved by complexing zinc with picolinic acid.

Introduction

Interest in human zinc nutriture is fostered by the growing evidence indicating that present dietary zinc frequently falls short of meeting the US RDA [1–3]. Marginal zinc nutriture is of concern because this essential trace mineral is involved in the functioning of over 100 enzymes, ranging from DNA and RNA polymerase to catalase and alcohol dehydrogenase [4]. Therapeutic applications of zinc range from its use in the treatment of acne vulgaris to stasis ulcers and acrodermatitis enteropathica.

Because of this potential need for zinc supplementation in the general population and for clinical applications it is important to determine what type of zinc is most efficiently absorbed. One possible approach to improving zinc nutriture in humans is suggested by the observation that the absorption of zinc is enhanced by a low-molecular-weight zinc-binding-ligand(s) (LMW ZBL), which appears to be produced in the pancreas [5]. The mechanism of its action in facilitating zinc uptake is not fully understood [6], although Johnson and Evans [7] have proposed that the ZBL complex facilitates intestinal transport of zinc and influences transport from plasma to various tissues. Several groups of investigators have suggested various compounds such as picolinate [8, 9, 10], citrate [11, 12, 13] and prostaglandins [14] as being the physiologic ZBL. These compounds have all been detected in

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pancreatic secretions [15]. They have also been reportedly found in human and rat milk, both of which contain a substance which promotes zinc absorption [16, 17].
The present study was designed to investigate the relative absorption of zinc in humans from various zinc complexes, with emphasis on two of the proposed LMW ZBL's – picolinic acid and citric acid.

Experimental

Materials and methods

Fifteen student volunteers enrolled in the project. All completed informed consent letters and the project was approved by the Human Subjects Review Committee of the College. All were in good health and showed no signs of zinc deficiency. Each individual completed a diet diary and health questionnaire prior to the study. These diaries indicated that dietary zinc (without supplements) was usually slightly less than the RDA. Participants taking mineral supplements discontinued them two weeks before the start of the trial. Each person was given a list of foods high in zinc and was asked to avoid these foods during the trial. No other dietary restrictions were imposed. Average daily dietary zinc intake (without project supplements) approximated 10 to 12 mg during the trial.
The design of this study was a double-blind four-period cross-over trial. The participants were randomly divided into four groups rotated through all of the following four-week supplementation periods (in randomly assigned order): zinc picolinate (144 mg complex); zinc citrate (146 mg complex); zinc gluconate (385 mg complex) and placebo (same tablet size as active); one group was assigned to each of the supplements each period. Each zinc complex daily regime contained 50 mg elemental zinc. There was a two week clearing period between each four week supplementation period during which no tablets were taken. Tablets were taken three times per day, midway between meals and just prior to retiring (decreasing exposure to stomach acids and phytates). The supplements were formulated and coded by General Nutriton Corporation Research Laboratories, Fargo, North Dakota.

Sample analysis

Zinc content of hair, urine, erythocytes and serum were measured in each subject the day before and the day after each period of supplementation by the following methodology.
Hair samples 1 to 1½ cm in length (minimum 0.4 gm) were cut close to the scalp from the occipitonuchal regions using stainless steel scissors. Care was exercised during each subsequent cutting to obtain new growth from the same area. The samples were sealed individually in opaque containers and stored in the dark prior to batch analysis.
Two-hour fasting blood samples were obtained by venipuncture from the antecubital fossa using a 10 cc zinc-free vacutainer (BD #6526). To minimize circadian rhythm variations, the blood for each period sample was drawn at the same approximate time of day (± 2 h) for each individual and for the group. The blood was centrifuged at high speed for 5 minutes to separate serum and erythrocytes. The serum was decanted into zinc-free containers and stored at 0 °C prior to batch analysis.
Urine samples were collected for a 24 h period, volume recorded and 10 cc removed for storage at 0 °C prior to batch analysis.

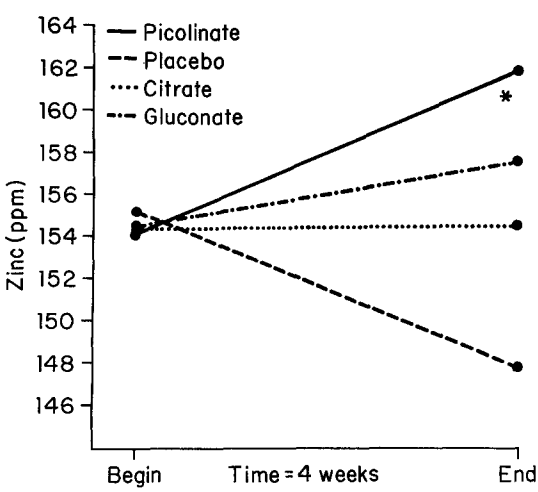

Figure 1
Changes in zinc level of hair after 4 weeks of supplementation with zinc picolinate, zinc citrate, zinc gluconate and placebo. Asterisk indicates significant change ($p < 0.005$).

The elemental analyses were performed with an Applied Research Laboratory (ARL) 34000 Vacuum Inductively Coupled Argon Plasma Emission Spectrometer (ICP). Up to 26 elements are measured simultaneously via data processing through a Burroughs 1900 computer [18, 19]. The ICP is calibrated with 6 standard solutions of different elements that are obtained from ARRO Laboratories, Joliet, Illinois. A control hair pool sample is run as every 50th specimen for the hair analyses, and at the beginning and end of a run with fewer numbers of samples of other specimen types. Daily coefficients of variations for the elements are below 10% [20]. The hair specimens were triple washed with a Triton solution and acetone and then air dried. A 0.4 g sample was then further processed for analysis. The hair (1.0 g) and blood (1.0 ml) specimens were then wet digested in a 3–2 nitric-perchloric acid mixture. Urine was treated with 1% nitric acid and incubated for 4 h at 85 °F. All specimens are centrifuged at 2000 × G for 5 m prior to aspiration and nubulization in the ICP. Urine and blood controls were obtained from ORTHO Diagnostic Systems in Raritan, New Jersey and were treated as normal specimens. All analyses were done in accordance with standards adopted by the American Society of Elemental Testing Laboratories.

Analytical methods

Paired t tests were used to identify statistically significant differences between mean values of changes and differences in change. Student's t test values were calculated by the computer program "Statistical Package for the Social Sciences". No analysis for cross-over effect was performed since beginning levels for each period were within expected null limits.

Results

Hair, urine, erythrocyte and serum zinc levels before and after administration of the four supplements are presented in Table 1. All levels were within the testing laboratories median reference range for adult humans.

Hair zinc level measurements

Figure 1 illustrates the changes in hair zinc levels during each four week period of administration.

Table 1
Zinc levels in human hair, urine, erythrocytes and serum before and after supplementation with zinc picolinate, zinc citrate, zinc gluconate and placebo.

Supplement	Zinc levels (ppm) in			
	Hair	Urine	Erythrocytes	Serum
Zinc Picolinate				
Before	154.1±3.1	0.33±0.02	9.01±0.3	5.67±0.2
After	161.0 4.2	0.59 0.06	10.83 0.4	5.75 0.2
Mean Change	7.8* $	0.26* $	1.82*$	0.08
Placebo				
Before	155.7±3.9	0.35±0.06	9.32±0.4	5.07±0.1
After	147.5 3.9	0.31 0.04	8.53 0.3	5.49 0.2
Mean Change	−8.2	−0.04	−0.79	0.42
Zinc Citrate				
Before	154.7±5.4	0.34±0.04	9.09±0.5	5.43±0.1
After	154.8 4.5	0.33 0.06	9.44 0.4	5.64 0.2
Mean Change	0.1	−0.01	0.35	0.21
Zinc Gluconate				
Before	154.3±4.2	0.34±0.07	9.06±0.4	5.47±0.1
After	157.7 3.4	0.46 0.05	8.48 0.4	5.46 0.1
Mean Change	3.4	0.12	−0.58	−0.01

* Significant change ($p < 0.005$).
$ Significantly different from placebo ($p < 0.002$).
Values presented as Mean ± SEM ($n = 15$).

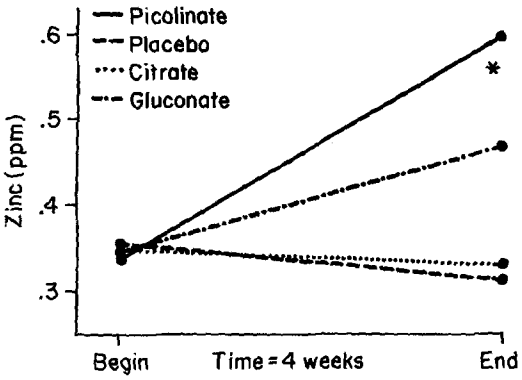

Figure 2
Changes in zinc level of urine after 4 weeks of supplementation with zinc picolinate, zinc citrate, zinc gluconate and placebo. Asterisk indicates significant change ($p < 0.001$).

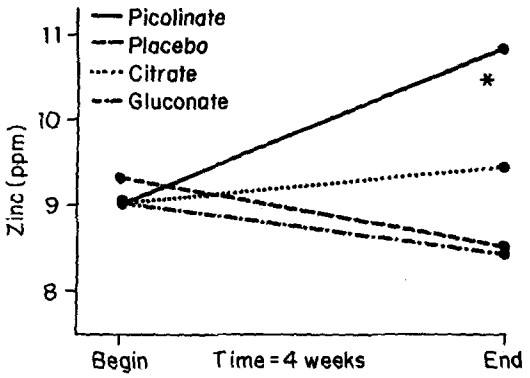

Figure 3
Changes in zinc level of erythrocytes after 4 weeks of supplementation with zinc picolinate, zinc citrate, zinc gluconate and placebo. Asterisk indicates significant change ($p < 0.001$).

Mean hair zinc values rose significantly (from 154.1 to 161.9 ppm, $p < 0.005$) during zinc picolinate supplementation. The difference in change during zinc picolinate versus placebo administration was significant (16.0 ppm, $p < 0.001$). Twelve of the fifteen individuals showed a significant increase; none showed a significant decrease during zinc picolinate supplementation. There was no significant change during zinc citrate or zinc gluconate trials.

Urine zinc measurements

Results from urine studies are shown in Figure 2. Urinary zinc excretion significantly increased following zinc picolinate administration (from 0.33 to 0.60 ppm, $p < 0.001$). The difference in change during zinc picolinate versus placebo was also significant (0.26 ppm, $p < 0.003$). All fifteen individuals showed a significant increase during zinc picolinate supplementation. There was no significant change in urinary zinc levels after the citrate or gluconate trials.

Erythrocyte zinc measurements

Figure 3 shows the erythrocyte zinc levels during each trial. Levels rose significantly when participants were supplemented with zinc picolinate (from 9.02 to 10.83 ppm, $p < 0.001$). The difference in change during zinc picolinate versus placebo was also significant (2.6 ppm, $p < 0.002$). Twelve of the fifteen participants showed a significant increase; while 1 showed a significant decrease during zinc picolinate supplementation. There was no significant change in erythrocyte zinc levels after either the zinc citrate or zinc gluconate forms.

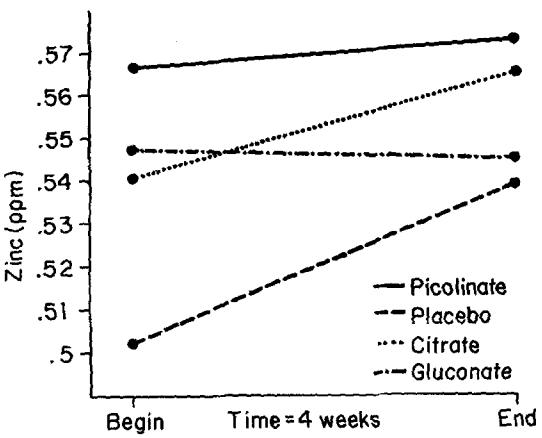

Figure 4
Changes in zinc level of serum after 4 weeks of supplementation with zinc picolinate, zinc citrate, zinc gluconate and placebo.

Serum zinc measurements

Serum zinc levels are presented in Figure 4. There were no significant changes in serum zinc during any of the trial periods although there was a statistically insignificant rise during the placebo

period (from 0.5 to 0.55 ppm) and zinc citrate period (from 0.54 to 0.56 ppm).

Discussion

The recent observations that a LMW ZBL apparently facilitates normal zinc uptake prompted this investigation into whether any of the proposed ZBL's would facilitate zinc absorption from a zinc supplement.

We found that, indeed, when zinc is orally administered as zinc picolinate, apparent absorption by 3 of our 4 measures is increased, while supplementation with zinc citrate, zinc gluconate or placebo showed no significant effect. To our knowledge, this is the first report describing an apparent increased zinc absorption in humans through the administration of extrinsic zinc complexed with a proposed ZBL. While this study does not address the question of the identity of the naturally occurring ZBL(s) in endogenous metabolism, it does show that there are differences in absorption for various exogenous zinc complexes.

Complexing zinc with picolinic acid (a bidentate chelating ligand which is a metabolite of tryptophan) appears to enhance zinc absorption in humans. This supports the work of Evans and Johnson [21, 22] who have previously shown that picolonic acid binds with zinc and promotes intestinal absorption of zinc in rats. Our work appears to show that picolinic acid promotes absorption of zinc in humans and further that it is superior to citrate or gluconate. Kreiger's [23] research indicates picolonic acid affects zinc metabolism through enhancement of intestinal absorption. Seal and Heaton [24] have recently reported in vitro and in vivo studies with rats indicating that added picolinic acid has the potential to enhance absorption of dietary zinc in the rat while citric acid does not, regardless of either acid occurring in milk. They found that uptake of $ZnCl_2$ across duodenal and ileal sacs was 4-fold greater when administered with 2-picolinic acid than with $ZnCl_2$ alone. Furthermore, absorption of zinc from $ZnCl_2$ plus zinc picolinate was 9 times greater than that from zinc citrate. Our results also support Lonnerdal and Hurley's [25] statement that there is as yet no evidence that zinc citrate plays a general role in adult intestinal zinc absorption, despite their evidence indicating that it is the zinc binding ligand in human milk.

The pattern of increases observed in hair, erythrocyte and urinary zinc levels with little increase in serum zinc after zinc supplementation are consistent with the findings of the in vivo kinetic studies of Babcock [26] that changes in serum zinc do not accurately reflect zinc nutritional status. As Babcock points out, the combined effects of zinc loading on gastrointestinal absorption, renal excretion and tissue deposition result in strong regulation of serum zinc concentrations. Their studies also showed that while there was a large increase in zinc absorption and renal excretion during loading, there was only a small increase in serum zinc. Sandstrom *et al.* [27] have also questioned the extent of changes in serum zinc corresponding with actual absorption. Short term serum levels can be a useful method for measuring the relative uptake of zinc after a single loading [28]. Serum zinc concentration appears to be a transient factor in the normal physiology of zinc absorption and storage [29, 30]. Miller and Stoke [31] have stated that zinc transfer from serum to biologically more active tissues is relatively fast, indicating rapid accumulation and turnover. The results of our study support the concept that the plasma system is indeed a temporary transport mechanism and not a useful measure of zinc nutritional status. It is our view that the rise in serum zinc levels during placebo administration may reflect mobilization and transport of zinc from rich to poor cells during minimal zinc dietary uptake. However, this rise may simply reflect the lower average initial values in this particular statistical set.

Hair zinc concentration is considered by some a useful measure of zinc status [32–35].

Bergman *et al.* [36] showed that hair zinc reflects past nutrition and dietary zinc intake. In our study, hair zinc levels changed over a four week period in the same manner as red blood cell content and urinary zinc excretion.

Conclusion

This study demonstrates that in humans zinc picolinate appears to be absorbed significantly better than zinc gluconate or zinc citrate. This finding may have practical value in situations where zinc supplementation is indicated. It would ap-

pear that since all 15 participants experienced all 4 supplementations, in varying sequences, the differences observed are not from individual variability nor the sample size.

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