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# Does Zinc Absorption Reflect Zinc Status?

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**Abstract:** Unlike iron, zinc absorption is influenced by dietary zinc intake, not zinc status. As dietary zinc increases, the total amount of absorbed zinc increases while the percent absorbed declines. The gastrointestinal tract maintains whole-body zinc homeostasis by adjusting endogenous zinc losses to the amount absorbed. At intakes below about 9 mg/day, zinc absorption occurs primarily by a saturable (carrier) process involving *ZIP4*, ZnT1, and other transporters. There is no evidence that past zinc intakes, or status, influences zinc absorption. Instead, current zinc intake is the chief determinant of zinc absorption. Supplemental zinc taken with water in the post-absorptive state initially is absorbed more efficiently than food zinc, but absorption efficiency declines within 24 hours presumably due to down-regulation of the zinc transporters. More research is needed to understand the effect of physiological state on zinc absorption.

**Key words:** Zinc, absorption, zinc status, zinc supplementation, zinc transporters

## Introduction

Studies in experimental animals and humans show that whole-body zinc concentrations remain relatively constant over a wide range of zinc intakes [1]. For example, weanling rats fed diets with zinc concentrations varying from 10 to 100 mg/kg diet maintained body zinc at about 30 mg/kg body weight [2]. This homeostatic adjustment to changes in dietary zinc is accomplished primarily by shifts in gastrointestinal zinc absorption and excretion. The capacity to adjust zinc absorption and excretion to changes in zinc intake lead many to assume that changes in zinc status, or tissue zinc levels, influences zinc absorption. If true, zinc absorption would increase when tissue zinc levels declines, irrespective of the amount of zinc ingested, to improve zinc status. It is well known that iron absorption increases when iron status is poor [3]. In the past, it was thought that the same is true for zinc. However, the effect of changes in tissue zinc status on zinc absorption is very small, if it exists at all [4]. The purpose of this paper is to review how zinc absorption and excretion change with current zinc intake rather than reflecting long-term intakes, or zinc status.

## Zinc absorption

Zinc absorption is defined in two ways: 1) the fraction (or percent) of zinc ingested that is absorbed (Fractional Zinc Absorption or FZA), and 2) the total quantity of absorbed zinc (TAZ) over an entire day [5]. FZA is determined by dividing the amount absorbed by the amount ingested. The fraction absorbed will depend on the bioavailability of the ingested zinc. If the diet is high in phytate, which binds zinc in the intestinal lumen and reduces its bioavailability, the FZA will be lower than if the diet is low in phytate. Typically, the FZA from a diet providing about 12 mg/day from highly available food sources will be about 0.4 or 40 %. The quantity of zinc absorbed, or TAZ, is the measure of physiological importance rather than

the FZA. The total quantity absorbed is determined primarily by the amount consumed and the bioavailability of the dietary zinc sources. The TAZ from a typical, highly available 12 mg/day zinc diet would be about 5 mg/day on the average.

Increases in dietary zinc have opposing effects on FZA and TAZ (Figure 1). If zinc homeostasis were 100 % efficient, the amount absorbed would equal the amount ingested until physiological needs are met. Thereafter, FZA would not change with increasing intake. Modeling zinc absorption data shows a different pattern [4]. The quantity of zinc absorbed only approaches 100 % at intakes below 1 mg/day. As the quantity ingested increases, the fractional, or efficiency of, absorption, declines. This pattern of zinc absorption is consistent with a saturable process of zinc absorption. In the 1980's, three different groups independently showed in experimental animals that zinc absorption into and across the enterocyte was saturable [6–8]. About 20 years later, this zinc absorption mechanism was finally appreciated in human nutrition when Miller and co-workers developed a mathematical model of zinc absorption using data from human studies [9]. Zinc absorption occurs primarily by a saturable mechanism up to about 7–9 mg of ingested zinc, which is close to the Estimated Average Requirement (EAR) for zinc, established by the Institute of Medicine for adult women and men, respectively, in 2001 [10]. Fractional zinc absorption declines rapidly with higher intakes, and the increase in total absorbed zinc is essentially linear suggesting that, at higher zinc intakes, absorption is occurring primarily by a non-saturable mechanism such as paracellular zinc diffusion between enterocytes [11].

The discovery of zinc transporters advanced the understanding of the mechanisms of zinc absorption [12]. *ZIP4* is primarily responsible for zinc uptake into the enterocyte. Other transporters, probably with lower zinc affinity, also facilitate zinc transport into the enterocyte since giving high oral doses of supplemental zinc effectively treats patients with acrodermatitis enteropathica. The intracellular trafficking pathways for zinc movement between the apical and basolateral sides of the enterocyte are not well defined. It appears that zinc may be sequestered in the cell by incorporation into the Golgi apparatus via ZnT7 [13] or binding to metallothionein [12]. At the basolateral membrane, ZnT1 transports zinc from the enterocytes into circulation.

Although iron absorption is directly related to the iron status of the host [3], this is not the case for zinc due to marked differences in iron and zinc homeostasis. Since the capacity to excrete iron is limited,

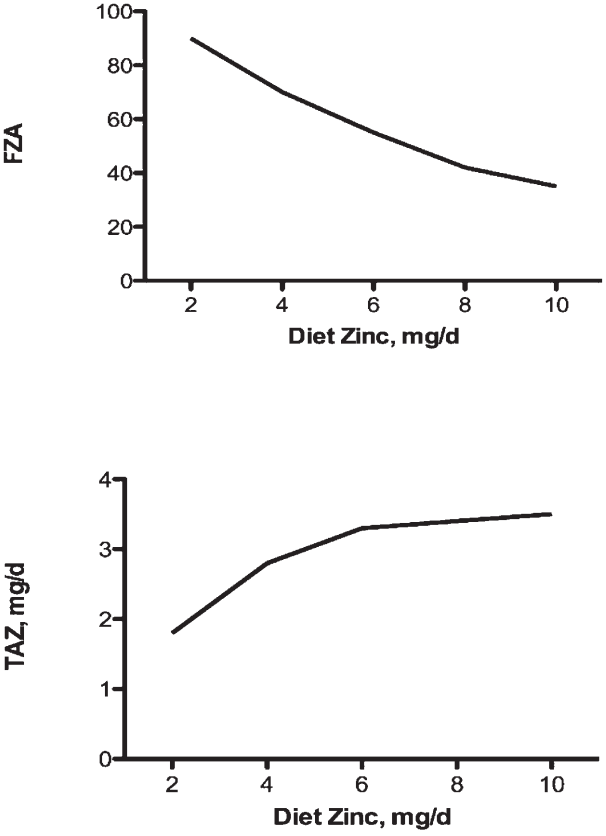


*Figure 1:* Effect of Dietary Zinc on Fractional and Total Zinc Absorption

the amount absorbed must be tightly regulated. This is not true for zinc. Zinc is readily excreted via the gastrointestinal tract and the kidney, making it unnecessary to tightly regulate zinc absorption. Second, the 24 different zinc transporters that up- and down-regulate cellular zinc uptake and efflux provide extensive flexibility in the capacity to regulate tissue zinc with varying zinc intake. Finally, it appears that a small cellular zinc reserve exists in all tissues, which is readily available to maintain function during short-term, insufficient intakes. With a subsequent increase in intake, a positive zinc balance occurs and the reserve is replenished. Thus, adjusting the excretion of absorbed zinc, rather than up- or down-regulating zinc absorption, maintains the cellular zinc reserve.

## The effect of past versus current zinc intakes on zinc absorption

In 1985, Wada and co-workers published the first study on the effect of a low zinc intake on zinc absorption and balance [14]. Six men confined to a metabolic unit were

fed 5.5 mg zinc/day for 54 days after consuming 16.5 mg/day for 12 days. Fractional and total zinc absorption was determined using an oral stable zinc isotope, $Zn^{70}$, and the fecal monitoring method. Fractional zinc absorption increased from 25 to 53 % ($p < 0.05$) and total absorbed zinc declined from 4.1 to 2.9 mg/day ($p < 0.05$) by the end of the second week of ingesting the low zinc diet. No further changes in fractional or total absorbed zinc were seen after consuming the low-zinc diet for six weeks. Zinc balance was achieved during the first week on the low-zinc diet due to a marked reduction in fecal zinc losses, and the men remained in balance thereafter for the entire period. Serum and urinary zinc did not change during the 54-day, low-zinc diet.

These data showed clearly that the efficiency, or percent, of zinc absorption increases with low intakes, but the total amount absorbed was 30 % lower than that absorbed when 16.5 mg zinc/day was ingested. Nevertheless, zinc balance was readily achieved due to a marked, rapid decrease in fecal zinc excretion, and serum zinc concentrations were maintained. These human data were consistent with research by two different groups showing that zinc absorption in experimental animals is primarily influenced by dietary zinc [6, 7]. Jackson and co-workers concluded "the quantity of Zn absorbed is proportional to the dietary Zn content over the normal range of intake, and Zn homeostasis is achieved through variation in Zn excretion [7]".

*Table I:* Effect of Past versus Current Zinc Intake on Zinc Absorption and Excretion in Rats[1]

| Diet Zinc | | Zn Absorption | Endogneous Excretion |
|---|---|---|---|
| Past mg/kg | Current mg/kg | % | µg/d |
| 1.5 | 3.6 | 88.2 | 7 |
| | 12.6 | 78.6 | 50 |
| | 20.5 | 63.6 | 98 |
| | 50.3 | 33.9 | 180 |
| 12.5 | 3.6 | 89.2 | 14 |
| | 12.6 | 73.0 | 72 |
| | 20.5 | 62.8 | 128 |
| | 50.3 | 33.5 | 232 |
| 50.3 | 3.6 | 92.8 | 14 |
| | 12.6 | 74.5 | 79 |
| | 20.5 | 51.9 | 122 |
| | 50.3 | 33.9 | 223 |

[1] Adapted from reference [17]

Coppen and Davies concurred; they reported that "at low doses, Zn homeostasis is achieved by changes in both the extent of Zn absorption and excretion [6]". Nevertheless, it was generally thought that longer-term zinc intakes of humans, or the individual's zinc status, affected FZA independently of the amount of zinc ingested. This misconception stemmed from the design of the human studies of zinc absorption; the efficiency of zinc absorption was higher in individuals consuming low-zinc diets, and who were presumed to be zinc-depleted [14–16]. A comparison of the effect of past and current zinc intakes on zinc absorption in rats in 1988 was ignored [17].

In that study, Johnson and co-workers compared the effects of past and current zinc intakes on zinc absorption and endogenous excretion [17]. Long-Evans, male rats, weighing 108 g initially, were fed diets containing 1.5, 12.6, or 50.3 mg Zn/kg diet for 19 days. Then each of those three groups was divided into four different dietary groups—3.6, 12.6, 20.5, or 50.3 mg Zn/kg diet and fed those diets for three weeks. FZA was measured by the isotope dilution method following an intramuscular injection of $Zn^{65}$. There was no evidence that past zinc intake influenced FZA. Instead, irrespective of the past diet, the FZA of animals currently fed only 3.4 mg/kg Zn/day was nearly three times higher than that of the animals receiving 50.3 mg/kg (Table I). The response of endogenous zinc excretion to past and current zinc intakes differed from that of FZA. Animals fed a very low zinc diet (1.5 mg/kg) previously excreted the least amount of zinc while consuming 3.6, 12.6, 20.5, or 50.3 mg Zn/kg diet. The authors concluded that zinc absorption is determined by current intake, but that zinc endogenous excretion is regulated by both current and past intake.

A similar study was not done in humans until 2008, when Chung and co-workers reported that current zinc intakes have a greater effect on FZA than does longer-term zinc consumption [18]. Fractional zinc absorption was measured from diets providing either 11 or 4 mg zinc/day on alternate days, using the dual stable isotopic tracer method in nine men at the end of a low zinc period (4 mg zinc/day for 6 weeks) and at the end of an adequate zinc period (11 mg zinc/day for 4 weeks). FZA was inversely related to current zinc intake with 61 % absorption from the low-zinc diet versus 36 % from the adequate diet, $p < 0.0001$, in both the low- and high-zinc periods. But, the total amount of absorbed zinc was higher from the 11 mg/day than the 4 mg/day diet, 3.6 vs. 2.5 mg/day, $p < 0.0001$. These findings in humans confirmed what had been observed in rats by Johnson and co-workers [17]: current zinc intakes determine zinc absorption, not past or long-term intakes.

The most comprehensive set of studies of zinc intake and absorption was done by Hunt and co-workers who studied 109 healthy men and women fed 10 different diets—5 low in phytate with phytate/zinc molar ratios ranging from 2–7 and 5 high in phytate with molar ratios ranging from 15–23. Data from the low-phytate diets provide information on the effect of zinc intake on absorption. After consuming the study diets for four weeks, FZA varied inversely with dietary zinc ($p < 0.0001$) whereas the amount absorbed increased with zinc intake ($p < 0.03$) (Table II). The study diet with the least amount of zinc provided 4.8 mg Zn/day; the other diets were marginal (7.4 mg/day) to adequate (11 to 18 mg/day) in zinc. As observed by Wada and Chung [14, 18], FZA exceeded 60 % with intakes below 5 mg/day, and it dropped to about 35 % when about 11 mg Zn/day was consumed. As expected, the FZA was only 37 % when 6.2 mg Zn was ingested from a high-phytate diet and 21 % from a 12 mg zinc, high-phytate diet. Potential biomarkers of impaired zinc status, including plasma zinc concentrations, were unresponsive to dietary zinc intakes.

It has been argued that experimental studies of the effect of diet on zinc absorption in animals and humans have been too short. In the real world, individuals chronically consume low zinc intakes for months or years. To determine if longer-term low zinc intakes alter the efficiency of zinc absorption, Lee and co-workers studied fractional zinc absorption in eight healthy men fed 4.1 mg Zn/day over a six-month period, after consuming 12.5 mg Zn/day for 4 weeks during the baseline period [15]. During the baseline period, FZA averaged 44 %. Two months after starting the low-zinc diet, FZA increased to 65 %, but total absorbed zinc decreased by one-half. After 4 months, FZA was 70 %, and it was 63 % after 6 months. The authors concluded that the decline from 70 to 63 % between 4 and 6 months reflected a decreased ability to sustain a high efficiency of zinc absorption over the long-term. However, the decline was not statistically different from absorption at 4 months. Further, the slight decrease in FZA between 4 and 6 months was associated with a decline in endogenous zinc losses. A study of zinc absorption in rural and urban Chinese women showed that those women chronically consuming about 5 mg zinc/day absorbed less zinc, 1.6 mg/day, than women chronically consuming 8 mg/day, who absorbed 2.75 mg/day ($p < 0.003$), but zinc balance was achieved by a concurrent reduction in fecal zinc losses, 1.3 versus 2.4 mg/day ($p < 0.001$), respectively. This study provides further evidence that zinc homeostasis is maintained in the long-term by adjusting endogenous zinc excretion to the amount of zinc absorbed over a wide range on zinc intakes.

In summary, zinc consumption affects FZA and TAZ differently. With increasing intakes, FZA declines whereas TAZ increases. None of the studies in animals and humans provide any evidence that short- or long-term past intakes (i.e. status) influence fractional or total zinc absorption. Instead, the efficiency and the amount of zinc absorbed are determined by current zinc intakes, and zinc homeostasis or balance is achieved by adjusting endogenous zinc losses.

## Zinc Absorption from Supplements

Supplemental zinc is widely used to replete individuals suffering from zinc deficiency or to prevent zinc deficiencies in vulnerable populations around the world. The specific choice of the supplemental zinc salt does not appear to be important [19]. However, unlike the response of plasma zinc to food interventions, supplementation with zinc salts causes a rapid, measureable increase in plasma zinc. An increase in plasma zinc occurred within 5 days when healthy, Zn-replete individuals were supplemented [20]. Plasma zinc concentrations also decline within a couple of days following withdrawal of the supplement. The timing and degree of the plasma zinc response did not differ between individuals given 10 or 20 mg supplemental zinc [20].

The marked increase in plasma zinc with zinc supplementation suggests a higher absorption of zinc from supplements than from meals, especially if the supplement is taken with water in a post-absorptive state. Tran and co-workers measured the relationship between the dose of supplemental zinc and zinc

*Table II:* Current Dietary Zinc and Zinc Absorption in Healthy Adults[1]

| Dietary Zn, mg/d | Fractional Zn Absorption, % | | Total Absorbed Zn, mg/d | |
|---|---|---|---|---|
| | Wk 4 | Wk 8 | Wk 4 | Wk 8 |
| 4.8 | 70 | 62 | 3.3 | 2.6 |
| 7.4 | 56 | 48 | 3.4 | 3.3 |
| 10.9 | 37 | 42 | 4.1 | 4.0 |
| 15.6 | 31 | 27 | 5.0 | 3.6 |
| 18.1 | 23 | 33 | 4.2 | 5.1 |

[1] Adapted from reference [30]

absorption when the supplement was taken in water in the fasting state in humans [21]. The amount of zinc absorbed increased progressively with increases in dose from 2.2 to 20 mg ingested zinc. However, a further increase from 20 to 30 mg supplemental zinc only increased the amount absorbed by 0.2 mg. This indicates that supplemental zinc is absorbed by a saturable, dose-response mechanism with intakes up to 20 mg; at higher levels absorption probably occurs by paracellular diffusion. The data imply that increasing the dose of supplemental zinc above 20 mg has little effect on zinc nutrition.

On the first day of zinc supplementation, 54 % of a 20-mg dose was absorbed [21]. On the next day, FZA declined to 34 %. Further, if the 20-mg supplement was taken orally for 6 consecutive days, the FZA on day 6 was only 24 %. These data suggest a down-regulation of zinc transporters involved in intestinal zinc absorption within 24 hours of taking a 20-mg zinc supplement. Beiseigel and co-workers also reported that postmenopausal women absorbed equivalent amounts of zinc, about 5 mg, after consuming diets providing either 14, 32, or 47 mg zinc/day for 16 weeks [22]. Given the rapid reduction in the efficiency of absorbing supplemental zinc, one may enhance total absorbed zinc more by giving the supplement weekly rather than daily.

To determine if the marked reduction in zinc absorption after two days of zinc supplementation is due to a down-regulation of intestinal zinc transporters, Cragg and co-workers measured the expression and protein levels of intestinal zinc transporters in biopsies from 18 ileostomy patients who were given 25 mg supplemental zinc/day or a placebo for 14 days in a cross-over design [23]. Zinc supplementation reduced the expression and protein content of ZnT1 in the biopsy samples. ZnT1 is the primary transporter for moving zinc across the basolateral membrane of the enterocyte into circulation. In addition, *ZIP4* protein levels, the transporter primarily facilitating zinc uptake by the enterocyte from the gut lumen, were reduced to undetectable levels. These data confirm in humans that intestinal zinc transporters respond readily to variations in dietary zinc, which in turn contribute to zinc homeostasis.

### Physiological Status and Zinc Absorption

The physiological status of the host is another factor that may alter zinc absorption to meet needs. During late pregnancy, lactation, and infancy or childhood, zinc needs rise to meet the needs for growth or milk synthesis and secretion. The effect of these increased demands on zinc absorption has not been studied sufficiently to draw firm conclusions about the effect of physiological state on absorption. One study in rats showed that the efficiency of zinc absorption increased on the last day (day 21) of gestation [24]. But, no studies of the effect of pregnancy on the expression of zinc transporters have been done to confirm that observation. Several studies in pregnant women show that the FZA is higher among women with lower zinc intakes [25, 26], but it is not known if this is due to an up-regulation of intestinal zinc transporters in response to need. Zinc absorption is also higher in lactating than in non-lactating, non-pregnant rats, but this is attributable to an increase in the absorptive surface of the small intestine [24]. It is unknown in *ZIP4* is up-regulated at the apical surface of enterocytes during lactation.

The data available on zinc absorption in infants and growing children are also limited. Studies of zinc transporter expression in human intestinal cell lines show that the capacity of the cells to regulate zinc absorption varies with the stage of cellular development [27]. Zinc uptake rates in undifferentiated cells were higher than that of differentiated cells. This may explain why infant zinc absorption does not appear to be as tightly regulated as that of adults. Studies of zinc absorption in human infants are limited. The few data available suggest that the efficiency of zinc absorption in premature and full-term infants is not up-regulated to meet higher needs [28]. After adjusting for differences in intestinal length and absorptive capacity, the efficiency of zinc absorption did not differ among term infants, preterm infants, and adults [29]. Further studies of the effect of host factors, such as infection or physiological state, on zinc absorption and homeostasis are needed.

## Conclusions

An understanding of zinc absorption provides the basis for evaluating the efficacy of the form and dose of zinc interventions. Zinc absorption is influenced by two factors—the quantity and source of ingested zinc. If the dietary zinc source is highly available, the quantity ingested is the major determinant of the amount absorbed. Unlike iron, long-term zinc intakes, or zinc status, do not influence zinc absorption. If the current intake is low, the efficiency of absorption is enhanced due to the presence of saturable, zinc transporters in the enterocyte. With higher intakes above the Estimated Average Requirement for zinc (~7–9 mg/day),

absorption efficiency declines, presumably due to carrier saturation. However, diffusion of zinc across the gut wall permits a small, gradual increase in absorbed zinc with increasing intakes, and balance is achieved by increasing zinc losses. In sum, zinc repletion following a previous low intake is achieved by reducing endogenous zinc losses, and the amount absorbed is determined by diet zinc rather than zinc status.

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