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Phytate Effect on the Absorption of Total Zinc in Zinc-Depleted Rats

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ABSTRACT

It has been known that dietary phytate decreases the absorption of body zinc pool which is composed of the dietary and endogenous zinc in the body. The purpose of this study was to examine the effect of phytate on the absorption of total bodyzinc in Zn-depleted rats. Rats were Zn-depleted with either low(0.8%) or high(1.6%) Ca diet containing sodium phytate for 4 weeks. After zinc depletion, rats were assigned into phytate or non-phytate dietary groups within each low- or high-Ca dietary group. Rat feces were collected for 2 weeks of the initial collection and 1 week after dietary crossover, during which the phytate and the non-phytate diet was switched over within the same Ca group. The content of Zn and Ca measured by atomic absorption spectrophotometer and phytate content was analyzed. Food intake was higher in the high Ca group than in the low Ca group($p<0.0001$), and was also higher in the non-phytate group than in the phytate group($p<0.0001$). Food intake and phytate level affected body weight gain in rats($p<0.0001$). Zinc excretion in the total feces was higher in the phytate group than in the non-phytate group at both low and high Ca level($p<0.0001$), except during the crossover collection period in high Ca group. Calcium, however, didn't show any synergistic effect on phytate effect($p<0.05$). This study showed that phytate decreased the absorption of total body zinc at both low and high Ca levels in Zn-depleted rats. A large portion of total body zinc originated from the endogenous zinc pool in these rats. The results of the present study showed the same effect of phytate on the endogenous zinc in Zn-depleted rats as in a previous study, confirming that phytate adversely affects zinc bioavailability, especially under marginal and poor zinc nutrition. (*Korean J Nutrition* 30(4) : 406~414, 1997)

KEY WORDS : phytate · zinc · calcium · bioavailability · Zn-depleted rats.

Introduction

The phytate effect on zinc absorption in humans was first identified in male adults in the Middle East in the early 1960s, due to their high phytate-containing diet[1-2]. The manifestations of zinc deficiency in animals include retarded growth and development, impaired reproduction, and poor immunity. Zinc deficiency also reduced neurosensory function including hypogeusia, nyctalopia, cognitive deficits, hair loss, thickening and hyperkeratinization of the epidermis, and testicular atrophy[3]. Comparison of dietary intake of zinc with requirements showed many women and children are at risk of deficiency, having low plasma levels of zinc with abnormal pregnancy outcomes in women and low iron nutrition with low zinc nutrition [4]. Today zinc deficiency is being recognized with great frequency every day and under various circumstances[5].

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Phytate(*myo*-inositol-1,2,3,5/4,6-hexakis dihydrogen phosphate) is one complexing agent which constitutes 1 – 3% by weight of all plant seeds, as well as many roots, tubers and certain fruits. Phytate has also been found in carrots and potatoes, but has not been demonstrated in onions, green, leafy or stem vegetables, or in the pulp of fruit[6,7]. It is the major storage form of seed phosphorus and usually occurs as a mixed calcium-magnesium-potassium salt in the aleurone of the grains. It is also known as a natural plant antioxidant that prevents oxidative injury[8]. The anionic character of phytate makes it ideal for forming complexes with mineral elements. Phytate is not absorbed and, therefore, anything binding to phytate would not be absorbed[9]. Thus, phytate has been considered as a chelator responsible for the poorer absorbility of dietary zinc[10-16]. However, Graf and Eaton[17] suggested a reevaluation for phytate's adverse effect because multiple factors might affect intestinal mineral absorption. They insisted that direct interference by phytate was still controversial. Their report showed that di- and trivalent cations form soluble complexes with phytate at high phytate-to-metal ratios, independent of pH. Calcium is also known as an antinutrient factor for zinc absorption along with the presence of phytate[18-21].

The total body zinc pool is composed of dietary zinc and endogenous zinc which mainly originates from pancreatic secretions. Endogenous zinc is almost three times that of dietary zinc intake[22-23]. Under Zn-depleted status, most of the total body zinc is from endogenous zinc secretion. A marginal zinc deficiency is common in daily diet, especially with diets low in animal protein and high in phytate-rich plant foodstuffs. It's important to invesigate effect of the phytate on total body zinc under zinc deficiency conditions, which can be a public health problem.

Thus, the present study investigated phytate effects on total body zinc absorption in Zn-depleted rats, and compared this effect on total body zinc with that on the endogenous zinc. The results of the phytate effect on the endogenous zinc in the Zn-depleted rats ras been previously reported[24]. Being with the examination of the effect of phytate on the absorption of total body zinc, this study also investigated the effect of calcium on the phytate effect.

Materials and Methods

1. Experimental design, diet, and animals

The experimental design was described in the previous experiment[24]. The two factors in this study were the two levels of phytate(for phytate and non-phytate group, 0 and 4.7g/kg, respectively) and two levels of calcium(for low Ca and high Ca group, 0.8% and 1.6%, respectively). Twenty-four young Sprague-Dawley male rats(Harlan Sprague Dawley Inc., Indianapolis) were used for each low and high Ca group (the initial mean body weight : 105±2g in low Ca group, 97±1g in high Ca group). All forty-eight rats were fed with a low-Ca, non-phytate diet for the first 3 wk of the growth period to get a certain body weight for the following body zinc depletion. During the next 4-week zinc depletion period, the rats in low Ca group were Zn-depleted with a low Ca, phytate-containing diet, and the rats of high Ca group with a high Ca, phytate containing diet. After 7 wk of growth and depletion periods, the Zn-depleted rats were reassigned to each phytate or non-phytate diet group within the same low or high Ca diet group. The rat feces were collected during the combined 3-wk collection period : 2-wk inital collection period, and 1-wk crossover collection period. The composition of the four experimental diets was also descibed in the previous report[24].

The animals were weighed weekly through the entire experimental period and food consumption was recorded daily during 3 wk of the collection periods.

2. Fecal sample collection and total Zn, Ca, phytate Analysis in the samples

The total rat feces was collected between about 2 : 00 p.m. to 4 : 00 p.m. daily during the combined 3 wk of the collection periods : 2 wk of the initial collection period and 1 wk of the corossover collection period.

Zn and Ca concentration in the diets and in the total feces were measured by a modified method of Anderson et al.[25]. All diets and feces samples were dry-ashed. After ashing, the samples were diluted with 10% nitric acid and were analyzed by using a Perkin Elmer Model 5000 atomic absorption spectrophotometer at

213.8nm wavelength(slit 0.7H, 15mA) with Zeeman background correction.

The accuracy of atomic absorption analysis and the completeness of digestion were verified by using the National Institute of Standards and Technology(NIST) peach leaves standard(standard reference material 1547). The zinc value found for the standard peach leaves(17.9μg Zn/g sample) with 98% recovery, compared well with the zinc value of the standard peach leaves(18.3μg Zn/g sample) reported by NIST.

For phytate analysis in the diets, a modification of the AOAC Official Method was used[26]. Phytate was extracted from duplicated samples of dried foods using diluted HCl. The extract was mixed with EDTA/NaOH solution and placed on an ion-exchange column. Phytate was eluted with 0.7M NaCl solution and wet-digested with a mixture of concentrated HNO_3/H_2SO_4 to release phosphate, which was measured colorimetrically. The amount of phytate in the original sample was calculated as hexaphosphate equivalent.

3. Statistical analysis

The statistical analytical system program SAS/STAT Version 6(SAS Institute Inc., Cary, NC) was used for statistical analysis. Analysis of variance(ANOVA) was performed as a 2×2 factorial treatment which is the main effects of phytate, calcium, and the interaction between phytate and calcium. Student's t-test was used for the comparison of total zinc concentration between the low Ca and high Ca group or between phytate and non-phytate groups. A $p<0.05$ or less was considered as having a significant difference.

Results and Discussion

1. Analysis of the diet composition

The concentration of Zn, Ca, and phytate are same as in the previous experiment[24]. The molar ratio of [phytate] : [Zn] was 32.3 in the low Ca, phytate group and 27.0 in the high Ca, phytate group. The molar ratio of [phytate]×[Ca] : [Zn] was 6.3 in the low Ca, phytate group and 12.3 in the high Ca, phytate group.

The rats used for this experiment had all been Zn-depleted for four weeks. Therefore, most of the total zinc analyzed in the feces might have originated from the endogenous zinc pool. If 10 of more molecules of phytate are consumed in the diet, one or more atoms of zinc from the diet and the endogrenous pool would be restrained from being absorbed/reabsorbed[7]. The molar ratios of [phytate] : [Zn] in the present study(32.3 for the low Ca, phytate group and 27.0 for the high Ca, phytate group) are high enough to produce zinc deficiency due to the phytate factor. Therefore, the molar ratios of [phytate] : [Zn] were also enough for the depletion of body zinc in rats. As the molar ratio of [phytate] : [Zn] in the diet increases, more Zn is depleted primarily from the endogenous pool in Zn-depleted rats.

2. Effect of phytate and Ca and food intake and body weight gain

The growth curves for the entire 10-week experimental period, including the 4-wk depletion period and the 3-wk collection period, is shown in Fig. 1. The very low zinc content of the experimental diets(6.2 – 6.8μg Zn/kg diet) and the addition of phytate produced a growth deficit. Even the inital body weight of the animals in the high Ca diet group was lower (97±1g) than that of the low Ca diet group(105±2g). The body weight in the high Ca group was greater than that of the low Ca group during the 4 wks of the depletion period($p<0.05$). The increases in body

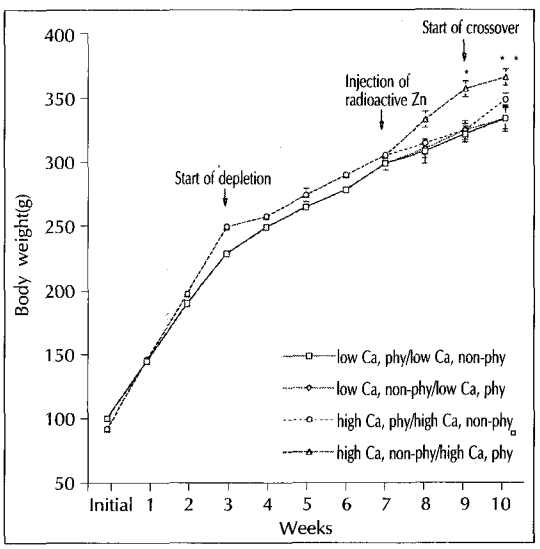

Fig. 1. Body weight growth of rats in relation to varying the dietary calcium and phytate. Values are means ±SEM ; n=12 per group. Growth period, initial to 3rd week ; depletion period, 3rd week to 7th week ; initial collection period, 7th week to 9th week ; crossover collection period, 9th week to 10th week.

weight continued into the collection period, during which the high Ca dietary groups with and without phytate(upper two groups) showed higher mean body weight than that of the low Ca dietary groups with and without phytate(lower two groups)($p<0.05$)(Fig. 1). High Ca, non-phytate group(the initial collection period)/high Ca, phytate group(the crossover collection period) showed the highest body weight($p<0.05$)(Fig. 1), due to the highest food intake(Table 1). The fact that high Ca groups showed higher body weight gain may be interpreted by a higher food intake in the high Ca dietary group than in the low Ca dieatry group during the whole 3 weeks of the collection period. During the initial collection period, mean food consumption of the high Ca group(17.9 ± 0.3g) was higher than that of the low Ca group(14.7 ± 0.2g)($p<0.0001$). During the crossover collection period, mean food consumption of the high Ca group (18.2 ± 0.4g) was higher than that of the low Ca group(16.1 ± 0.2g)($p<0.0001$). Mean food intake of the four dietary treatment groups is shown in Table 1.

The growth curves clearly showed the effect of phytate on body weight gain. In Fig. 1, the high Ca, non-phytate group(above one in upper two groups) showed higher body weights than the high Ca, phytate group(below one in upper two groups)($p<0.05$) during the initial collection period. This result shows the adverse effect of phytate on a zinc deficient diet on the rat body growth rate. In the low Ca group, there is no statistical difference between the phytate group and the non-phytate group. During the following 1 wk of the crossover collection period, in which phytate and non-phyate diets were switched over within each dietary Ca group, the same pattern appeared. The high Ca, non-phytate group(below one in upper two groups) showed a sharper or body weight gain than the high Ca, phytate group, and the same pattern as in the low Ca group(without statistical significance). This implies that phytate decreases the body weight gain by affecting zinc nutrition. Calcium did not affect body weight gain in the rats in this experiment. Actually, the high Ca group didn't show higher body weight gains during the depletion and collection periods(Fig. 1). However, food intake affected the body weight gain, and the phytate content in the diets showed a growth depressing effect.

Table 1. Effect of dietary Ca and phytate level on food intake of rats(g diet/day/rat)[1,2]

Dietary group	Initial collection period[3](2 wks)	Dietary group	Crossover collection period[4](1 wk)
Low Ca, phytate	13.9 ± 0.3^a	Low Ca, non-phytate	16.1 ± 0.3^a
Low Ca, non-phytate	15.5 ± 0.2^b	Low Ca, phytate	16.1 ± 0.2^a
High Ca, Phytate	15.9 ± 0.5^b	High Ca, non-phytate	16.5 ± 0.4^a
High Ca, non-phytate	19.9 ± 0.5^c	High Ca, phytate	19.8 ± 0.5^b

1) Values are means±SEM of twelve rats in each group (g diet/rat/day)
2) The effects of calcium and phytate among treatment means analyzed by Tukey's *Studentized range* test. Values with different superscript within the same column are significantly different at $p<0.05$
3) Ca effect($p<0.0001$), phytate effect($p<0.0001$), Ca and phytate interaction($p<0.0099$)
4) Ca effect($p<0.0001$), phytate effect($p<0.0011$), Ca and phytate interaction($p<0.0009$)

At the beginning of the zinc pool depletion in rats, the mean body weight in the low Ca dietary group was 228 ± 4g, and that of the high Ca dietary group was 248 ± 3g, which means the animals were not very young at the time of zinc depletion. By starting with mature rats, the effect on body weight by zinc nutrition might not be as serious as on young rats. However, in older rats, body zinc depletion would be efficient for the test of zinc absorption.

3. Phytate effect on total Zn concentration in the feces

The statistical data summary showed a large effect due to phytate levels on the absorption of total zinc (Table 2). Total zinc excretion in the feces was affected by the presence of phytate in the diets at both low Ca and high Ca levels. In the Zn-depleted rats, only a small portion of total body zinc excreted in the feces originated from the endogenous zinc pool.

Within each low Ca and high Ca group : The effect of dietary phytate on total zinc concentration in the feces is shown in Table 2 and Fig. 2. In the low Ca dietary groups, analyzed mean fecal Zn excretion during the initial collection period was higher in phytate group($85.81\pm1.23\mu$g Zn/total feces/day) than in non-phytate group($52.61\pm1.36\mu$g Zn/total feces/day) ($p<0.0001$). During the crossover collection period,

the analyzed fecal Zn excretion was higher in phytate group(71.39±1.19μg Zn/total feces/day) than in non-phytate group(48.99±2.05μg Zn/total feces/day)($p<0.0001$), too(Table 2 and Fig. 2). The addition of phytate to the diet decreased the absorption of zinc and caused higher fecal zinc excretion during the initial collection period and the dietary crossover collection period in the low Ca group.

For the high Ca dietary groups, analyzed fecal Zn excretion during the initial collection periods was higher in phytate group(60.89±0.90μg Zn/total feces/day) than in non-phytate group(32.27±0.92μg Zn/total feces/day)($p<0.0001$). During the crossover collection period, however, analyzed fecal Zn excretion was higher in non-phytate group(53.72±1.70μg Zn/total feces/day) than in phytate group(32.05±1.57μg Zn/total feces/day)($p<0.0001$)(Table 2 and Fig. 2). The phytate effect which was shown during the crossover collection period in high Ca group implies the presence of two endogenous zinc pools under Zn-depleted conditions : one is stable zinc pool that is not affected by phytate and the other is a labile zinc pool that is affected by phytate[27]. Most of the zinc precipitated with phytate is primarily from the labile endogenous zinc pool. Once the labile zinc pool is depleted by the high phytate content, the phytate effect may not be apparent on total zinc absorption any more. It can be interpeted that the phytate group in the high Ca group showed lower total zinc excretion in the feces rather than in the non-phytate group(Fig. 2). This result exactly agreed with previous studies of the phytate effect on the endogenous zinc in Zn-depleted rats[24].

Table 2. Effect of dietary phytate and Ca on total Zn concentration in the feces

Dietary group (Initial collection period)[3]	(2 wks)	Dietary group (Crossover collection period)[4]	(1 wks)
Low Ca, phytate	85.81±1.23[a]	Low Ca, non-phytate	48.99±2.05[a]
Low Ca, non-phytate	52.61±1.36[b]	Low Ca, phytate	71.39±1.19[b]
High Ca, Phytate	60.89±0.90[c]	High Ca, non-phytate	53.72±1.70[d]
High Ca, non-phytate	32.27±0.92[d]	High Ca, phytate	32.05±1.57[a]

1) Values are means±SEM of twelve rats in each group (g diet/rat/day)
2) The effects of calcium and phytate among treatment means analyzed by Tukey's *Studentized range* test. Values with different superscript within the same column are significantly different at $p<0.05$
3) Ca effect($p<0.0001$), phytate effect($p<0.0001$), Ca and phytate interaction($p<0.0099$)
4) Ca effect($p<0.0001$), phytate effect($p<0.0011$), Ca and phytate interaction($p<0.0009$)

The results of the present study agreed with many previous reports that phytate decreases the absorption of zinc, decreasing the absorption and rebasorption of dietary and endogenous zinc[1)28-32)]. Phytate-containing diet(4.7g/kg diet)s decreased the absorption of total body zinc at both low Ca and high Ca level. Even during the dietary crossover collection period, in which phytate and non-phytate diet was switched over within the same Ca level, the phytate group showed higher fecal zinc excretion.

The first descriptions of clinical zinc deficiency were in Iranian villagers. Its occurrence in spite of reasonable amounts of zinc in the village diet and was attributed to the binding of dietary zinc to the high fi-

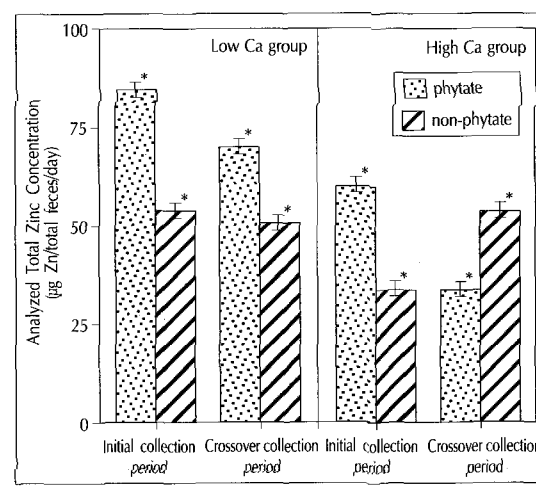

Fig. 2. Fecal excretion of analyzed total Zn concentration in low Ca and high Ca group during the collection period. The entire collection period was 2 wks of the initial collection period and 1 wk of the crossover collection period. Values are mean±SEM of analyzed total Zn concentration during each collection period(n=12 rats per group). Each rat feces was collected daily during each collection period. Total Zn concentration was analyzed by atomic absorpion spectrophotometer. Bars that have asterisk (*) are significantly different at $p<0.05$ between phytate group and nonphytate group during each collection period. Paired t-test was used for the comparision of total Zn concentration between phytate group and non-phytate group in each collection period.

bre, high phytate village bread, *tanok*[1]. In a study using meals prepared from four different cereals and extrinsic labeling with ^{65}Zn, the defected absorption of labaled zinc was negatively correlated to the phytate content of the meal[15]. Therefore, food preparation that decreases the phytate content can improve zinc absorption. A greater fall in plasma zinc and a reduced growth rate have also been observed in a soy-based diet than in a milk-based regimen, which indicates that the bioavailability of zinc could be a problem in high-phytate soybecan diets[29]. In the zinc tolerance test as a measure of zinc absorption, the depression of the plasma zinc response to an oral zinc load by a high fiber, reduced phytate concentrated wheat fiber preparation was significantly less than the depression produced by standard wheat bran[30]. Standard raw wheat bran totally abolished the plasma zinc response that was obtained when zinc was given alone, suggesting a low absorption of zinc due to the high phytate content of standard wheat bran. Nävert et al.[31] also found that zinc absorption from bread containing bran increased when the phytate content was reduced. In a study by Sandberg et al.[32], wheat bran significantly reduced zinc absorption in patients but there was no correlation between the ileostomy phytate phosphorus and zinc outputs, suggesting perhaps that an additional factor was contributing to zinc binding. With the result of the present study, clearly the reduction of phytate in the diet can lead to improved zinc absorption.

4. Ca effect on total Zn concentration in the feces

Within each phytate and non-phytate group : Analyzed mean fecal zinc excretion was higher in the low Ca group(85.81±1.23μg Zn/total feces/day) than in the high Ca group(60.89±0.90μg Zn/total feces/day) during the initial collection period, and was also higher in low Ca group(71.39±1.19μg Zn/total feces /day) than in high Ca group(32.05±1.57μg Zn/total feces/day) during the crossover collection period($p<0.0001$), too(Fig. 3).

Analyzed Zn excretion in the feces was higher the in low Ca, non-phytate group(51.61±1.36μg Zn/total feces/day) than in the high Ca, non-phytate group (32.27±0.92μg Zn/total feces/day) during the initial collection period($p<0.0001$), however, no statistical difference was shown during the crossover collection period(Fig. 3).

Fecal zinc excretion was higher in the low Ca group than in the high Ca group during both the initial and crossover collection within phytate group, and during the initial collection period within the non-phytate group. Even before zinc was implicated in the deficiency syndrome, it was known that diets containing calcium in excess of the amount considered adequate apparently accentuated the syndrome ; high levels of calcium decreased zinc absorption and availability. In the present study, however, a high calcium diet didn't act as the synergizing factor for phytate's adverse effect on zinc absorption in the phytate group(Fig. 3). The analyzed total fecal zinc was higher in the low Ca group than in the high Ca group during the initial collection period and the cross-over collection period at both phytate and non-phytate levels. Early work by Byrd Matrone[33] showed that at high concentrations of calcium, calcium competed for binding sites on the phytate molecule, which reduced the amount of zinc that precipitated. It was also suggested that the level

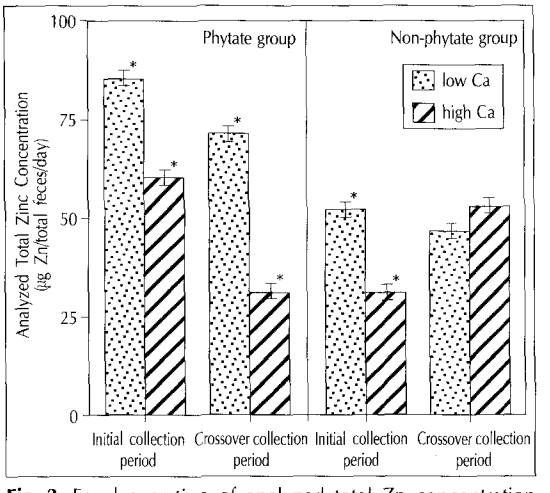

Fig. 3. Fecal excretion of analyzed total Zn concentration in phytate group and non-phytate group during the collection period. The entire collection period was 2 waks of the initial collection period and 1 wk of the crossover collection period. Values are mean± SEM of analyzed total Zn concentration during each collection period(n=12 rats per group). Bars that have asterisk (*) are significantly different at $p<0.05$ between low Ca group and high Ca group during each collection period. Total Zn analysis and statistics are same as in Fig. 2.

of phytate was critical on forming insoluble phytate-Ca-Zn complexes. Calcium ions only potentiated zinc ion precipitation at high concentration of phytate, high [phytate] : [Zn] ratios. At low [phytate] : [Zn] ratios, calcium ions competed with zinc inos for binding sites. The larger the concentration of calcium ions, the larger the extent of potenitation of competition, which makes less insoluble phytate-Ca-Zn complexes, and less unabsorbed zinc in the feces[33]. Therefore, the fact that the low Ca, phytate group showed higher fecal zinc excretion than that of the high Ca, phytate group can be explained with the potential competition of calcium for the binding site on phytate. This can facilitate zinc being more soluble and absorbed at high calcium concentration at fixed phytate level. The rats used for this experiment were all Zn-depleted during 4 wks, and were fed with a Zn-deficient diet during following 3 wks of the collection period. Zinc status was very poor and high calcium concentration in the diet could compete with the low zinc levels for binding to phytate. This causes the high Ca, phytate group to render more soluble zinc ions, resulting in lower fecal zinc excretion than from the low Ca, phytate group.

Since phytate is a natural and normal constituent of plant foodstuffs and has such a marked effect on zinc availability, a better understanding of phytate is necessary. It was shown that the phytate of natural foodstuffs was more resistant to breakdown than that added to casein diets[34]. This implies a more significant zinc deficiency in men eating the normal diets than that in lab animals fed semi-purified casein-based diets. The phytate present in a complex is resistant to enzymatic breakdown. This phytate complex may be in association with protein. Phytate was very closely associated with protein at and below the isoelectric point of protein. Above the isoelectric point, phytate was dissociated more rapidly than the protein was solubilized[35]. Phytate is contained in plant proteins, but not animal proteins, and thus was implicated in the lower zinc availability to animals fed plant protein than to those fed animal protein diets[12]. Evidence indicates that insoluble and nonabsorbable zinc phytate complexes are formed in the gastrointestinal tract, which renders the zinc unavailable. Other polyphosphates, namely hexametaphosphate, acid pyrophosphate, and tripolyphosphate, have been shown to similarly affect zinc availability[36]. Though these polyphosphates are not present in natural foodstuffs, they enter into the human food chain in processed foods.

One of the modern dietary guidelines to prevent some adult diseases is the high intake of the dietary fiber food and plant food sources. Most of the high fiber foods also contain high amounts of phytate, which can adversely affect zinc bioavailability[7]. In the developing countries and some areas in which the diet is generally composed of high levels of cereal products and plant food stuffs, zinc deficiency may become a public concern ; marginal zinc deficiency is already in common among the large populations. Even in Western diets, with the higher intake of the animal foods than in the developing countries, phytate contents in the diet from the cereal products and any other plant food sources may still cause insufficient zinc intake for RDA. Current RDA for zinc requirements do not take into account antagonistic factors for zinc absorption. The content of phytate in prepared infant cereals and soybean-based formulae indicates that, if these constitute the majority of the dry matter of an infant's diet, zinc supplementation might be advisable. The establishment of the essentiality of zinc should also consider phytate, and its effects on zinc bioavailability. It has been found that actually, almost all foodstuffs contain several times more zinc than would be necessary to meet the requirement established for a rat[37]. There is an apparent difference between analytical content and nutritional requirement. Therefore, the common public zinc deficiency in the developing countries and even in the developed ones, and the present nutritional policy in which zinc cannot be supplemented to human foodstuffs, means that zinc can easily become the first limiting nutrient.

With the present and the previous study of the phytate effect on endogenous zinc, there remains little doubt that phytate in animal diets markedly decreases the bioavailability of zinc for absorption/reabsorption from dietary and endogenous sources. The wide distribution of phytate in foodstuffs from plant sources indicates that phytate, as well as zinc, must be considered in nutritional studies of zinc metabolism.

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