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Dietary phytate, zinc and hidden zinc deficiency

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ABSTRACT

Epidemiological data suggest at least one in five humans are at risk of zinc deficiency. This is in large part because the phytate in cereals and legumes has not been removed during food preparation. Phytate, a potent indigestible ligand for zinc prevents it's absorption. Without knowledge of the frequency of consumption of foods rich in phytate, and foods rich in bioavailable zinc, the recognition of zinc deficiency early in the illness may be difficult. Plasma zinc is insensitive to early zinc deficiency. Serum ferritin concentration $\leq 20\,\mu g/L$ is a potential indirect biomarker. Early effects of zinc deficiency are chemical, functional and may be "hidden". The clinical problem is illustrated by 2 studies that involved US Mexican-American children, and US premenopausal women. The children were consuming home diets that included traditional foods high in phytate. The premenopausal women were not eating red meat on a regular basis, and their consumption of phytate was mainly from bran breakfast cereals. In both studies the presence of zinc deficiency was proven by functional responses to controlled zinc treatment. In the children lean-mass, reasoning, and immunity were significantly affected. In the women memory, reasoning, and eye-hand coordination were significantly affected. A screening self-administered food frequency questionnaire for office might help caregiver's identify patients at risk of zinc deficiency.

Introduction

Epidemiological data suggest at least one in five humans are at risk of zinc deficiency [1]. The main causes are frequent consumption of foods high in phytate and other indigestible zinc binding ligands, and infrequent consumption of foods high in bioavailable zinc, such as red meat. As a result zinc deficiency occurs throughout life.

High intakes of phytate and low intakes of red meat probably became problems for most humans about 10–12,000 years ago as agriculture evolved. Solomons [2] suggested, "at no time during the last 400 generations has either the intake of zinc or its bioavailability been as high as it was for the 10,000 generations that preceded it." Fortunately, technologies for preparation of plant seeds to an editable form, such as milling and fermentation also evolved. Removal of phytate and other zinc-binding plant ligands, and more recent modern fortification can improve the quality of plant based foods. Thus, the biological non-adaptation to dietary phytate [3–5] is potentially not a problem.

Phytic acid, D-myo-inositol (1,2,3,4,5,6) hexakisphosphate [6] is a component of all seeds that binds di- and tri-valent metals to form phytates. Reinhold et al. [7–10] showed the binding of zinc by phytate and other metal binding ligands in Iranian rural flat bread and suggested it was one of the causes of zinc deficiency. They also showed that the phytate rich diets of poor Iranians [7] contained as much zinc as the omnivorous diets of affluent Iranians and Americans.

Hunt et al. [5] used whole diets, ^{65}Zn tracers and whole-body counting to show the high impact of phytate on zinc utilization of 109 US adults. Omnivorous diets provided a range of zinc and phytate intakes. Each subject was fed one of ten diets that provided 4.3–18.2 mg zinc/2500 kcal. Red meat provided highly bioavailable zinc. Phytate sources were: maize, wheat cereal, wheat germ, whole wheat bread, whole-wheat pasta, wild rice, refried beans, garbanzo beans, green beans, peas, soy based meat substitute, peanut butter, sunflower seeds, pecans, and cashews. The 5 low phytate diets had phytate:zinc molar ratios of 1.6–6.7; in contrast the 5 high phytate diets had phytate:zinc molar ratios of 14.6–22.9. Zinc absorption occurred at all levels of zinc intake when phytate was low, but was suppressed, regardless of zinc content, when the phytate was high. Relevant to the potency of phytate Hambidge et al. [11] reported that for each 1000 mg of phytate added to their experimental diet the amount of zinc needed for homeostasis roughly doubled.

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Given the above knowledge, it is, in retrospect, remarkable that human zinc deficiency was thought unlikely by nutrition experts until 1961 when Prasad et al. [12] reported putative zinc deficiency in 12 stunted, hypogonadal, iron deficient farmers, aged about 16–20 years, from near Persepolis, Iran. Prasad in Egypt and Halsted in Iran confirmed the hypothesis through zinc treatment trials and other findings [13].

In nature human zinc deficiency occurs in the context of adequacy other nutrients and other diseases. In populations physical signs consistent with deficiency usually are evident in relatively few individuals. The signs are a signal that many others are also affected, though not obviously. This type of deficiency has been called "subclinical" or "mild", terms that imply a level of importance. In truth, the severity is unknown. A more neutral term, "hidden" might be preferred. Usually patients, family and caregivers are unaware of illness. Given that the cause is dietary, qualitative frequency of consumption of common foods might reveal individuals at risk.

Experiments

Here we use data from 2 studies to examine "hidden" zinc deficiency.

Three hundred fifty-nine 1st and 2nd grade Mexican-American children, aged 7–9 years, from low-income districts of Brownsville, TX were studied. With a few exceptions they had no complaints, and their parents and the school nurses considered them well. Their home diets were based on traditional rural-Mexican foods. All had full access to free breakfast and lunch at school. Food frequency interviews with caregivers responsible for meals found maize and/or wheat tortillas, and frijoles, were respectively served ≥ 5 times per week to 49, 33 and 42%, and ≤ 1 time per week to 29, 41 and 24%. Red meat was served to 15% ≥ 5 times per week and ≤ 1 time per week to 40%; chicken was served to 53% ≥ 5 times per week and ≤ 1 time per week to 14%.

With few exceptions all subject appeared well. The Height:Age Z score was −0.438, range −2.62 to 2.74; 16 boys and 2 girls had Z scores ≤ -2.0. The Weight:Height Z score was 1.413, range −1.6 to 10.0. Plasma zinc concentration of 353 subjects after an overnight fast (mean ± SD) was 14.72 ± 2.14 μmol/L; 13 had concentrations <10.7 μmol/L. Hair zinc concentration, a biomarker not commonly measured, was below the 1.68 μmol/g cut-off suggested by Gibson et al. [14–16]. The 317 subjects had a mean occipital hair zinc concentrations of 1.63 ± 0.52 μmol/g. The 150 boys had concentrations of 1.806 ± 0.512; in contrast, the 167 girls had concentrations 1.468 ± 0.473 μmol/g ($P < 0.001$).

Treatment effects of zinc were measured by a 10-week double blind, randomized trial of 20 mg zinc (as zinc sulfate) given with a broad mixture of other micronutrients (ZM), 24 mg iron (as ferrous sulfate) given with the micronutrients (FM), the other micronutrients alone (M), and placebo (P).

Growth by percentage change in lean mass (by bioelectrical impedance) was significant after treatment (ANOVA, $P < 0.014$) in the 92 girls with baseline hair zinc concentrations ≤ 1.68 μmol/g [17]. Group comparisons (Games-Howell test, $P < 0.05$) found ZM > M and FM. Reasoning of the 182 subjects tested, was measured by the percentage change in number of trials needed to identify oddity [18,19]. The treatment effect was significant (ANCOVA, $P < 0.002$; co-variables: after treatment plasma zinc concentration, baseline hair zinc concentration, baseline serum ferritin concentration). Group comparisons (Bonferroni test, $P < 0.05$) found ZM > P. In the 136 subjects with baseline plasma zinc <75th percentile treatment was significant ($P < 0.001$) and ZM > M ($P < 0.05$). Immune functions were measured in 48 first graders treated with ZM or M [20]. Fasting morning plasma zinc was 14.9 ± 1.7 μmol/dL, and hair zinc was 1.78 ± 0.52 μmol/g, with 41.6% ≤ 1.68 μmol/g. Serum ferritin was 25.7 ± 18.6 μg/L, with 50.0% ≤ 20 μg/L. Outcomes included lymphocyte ratios $CD4^+$:$CD8^+$and $CD4^+CD45RA^+$:$CD4^+CD45RO^+$; *ex vivo* mitogen stimulated generation of IL-2, INF-γ, and IL-10 by peripheral blood monocytes; and plasma concentrations of interleukin-1 receptor antagonist (sIL-1ra) and soluble tumor necrosis factor receptor 1 (sTNF-R1). Treatments were ZM and M. Paired t-tests showed that M did not significantly increase the ratio of $CD4^+CD45RA^+$:$CD4^+CD45RO^+$, the generation of IL-2 and IL-10, and the plasma concentration of sTNF-R1. ANCOVA (potential covariates were concentrations of plasma zinc before and after treatment, hair zinc before treatment, and serum ferritin before treatment) showed ZM > M for all indexes except the ratio of $CD4^+$:$CD8^+$.

Zinc nutriture was studied in 129 premenopausal women, aged 19–39 years from the Galveston, TX area [21]. They had no health complaints, had not recently consumed nutrition supplements, had regular menses with a 24–34 day cycle, had completed high school, had incomes $\geq 2\times$ the poverty standard, appeared normal by physical examination and had normal screening laboratory screening tests including hemoglobin. A brief screening food frequency found that 65 infrequently ate red meat; their serum ferritin concentrations were ≥ 5 and ≤ 18 μg/L. A more complete self-administered food frequency [22] examined a wider array of common foods. The frequencies of beef, vitamin C-fortified drinks, orange juice, eggs, yoghurt, milk, coffee, tea, beans and bran breakfast cereals were subsequently used, with the frequency of bleeding through menstrual pads, as potential predictors of zinc status. Zinc status of the first 50 was measured by 24-h three compartment mammillary model of zinc kinetics, using ^{67}Zn and the analysis of specimens of plasma by inductively coupled isotope ratio (with ^{68}Zn) mass spectrometry. Thirty-three of the 50 subjects were not taking contraceptives. Their data showed that six foods and menorrhagia predicted the size of the lesser peripheral zinc pool (Table 1). In addition there was a non-linear correlation ($n = 28$; $R^2 = 0.891$; $P < 0.001$) between the concentration of serum ferritin and the size of the lesser peripheral zinc pool, with a breakpoint at 21 μg/L.

Cognitive outcomes were measured by computerized tasks at baseline, and after 8 and 16 weeks of treatment in the 65 iron deficient subjects, on days 8–12 of the menstrual cycle. Assignment was random and double blind. The three treatments included, a broad mixture of micronutrients (M) at 50% of the 1989 RDA, 30 mg zinc (as sulfate) with M, and 30 mg ferrous iron (as sulfate) with M. Nineteen subjects were assigned M which was administered for 8 weeks then pseudo-switched and then administered for 8 more weeks. Two groups of 23 subjects were assigned to ZM or FM, which were administered for 8 weeks, then switched and administered for 8 more weeks. Treatment effects (ANOVA) were significant for memory, $P < 0.04$; reasoning to identify oddity, $P < 0.03$; perception, $P < 0.02$; and eye-hand coordination for circular tracking, $P < 0.007$. Group comparisons by the Tukey–Kramer test ($P < 0.05$) found the % correct memory of an object after ZM > FM; the reaction time of the reasoning task was shorter (desirable) after ZM compared to M; the reaction time for perception was shorter after FM (desirable) compared to M; and correct circular tracking after ZM and FM > M.

Discussion

The clinical importance of "hidden" zinc deficiency has received little attention. Because thresholds for deranged functions are unknown, caution is prudent. Some examples of functions at risk are: gene expression [23], fetal growth and development [24,25], child and adolescent growth [13,26], wound healing [27–29],