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МЕТОДИЧЕСКАЯ СТАТЬЯ

COOKIES FORTIFIED WITH ZINC AND MULTI-MICRONUTRIENTS. PROPOSED MICRONUTRIENT FORTIFICATION OF A SPECIAL FOOD FOR PREVENTION AND/OR TREATMENT OF HUMAN ZINC DEFICIENCY

ВЫПЕЧКА, ОБОГАЩЕННАЯ ЦИНКОМ И КОМПЛЕКСОМ МИКРОНУТРИЕНТОВ. СХЕМА СОЗДАНИЯ СПЕЦИАЛИЗИРОВАННОГО ПРОДУКТА ДЛЯ ПРОФИЛАКТИКИ И/ИЛИ ЛЕЧЕНИЯ ДЕФИЦИТА ЦИНКА У ЧЕЛОВЕКА

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ABSTRACT: Zinc deficiency is a world-wide problem that appears to affect nearly 50% of humans. Young children are at increased risk of zinc deficiency because of their relatively high requirements for growth and other aspects of development. Risk is especially common among the poor who often subsist on diets low in flesh foods and based on foods of plant origin that are rich in indigestible zinc binding plant ligands such as phytate and certain fibers. A potential solution to this problem is fortification of special foods such as cookies with zinc and a broad mixture of micronutrients that cooperate with zinc in metabolism. Here we describe such a product and suggest a potential research protocol for evaluation of efficacy of cookies in children or other at risk groups.

РЕЗЮМЕ: Дефицит цинка представляет собой глобальную проблему, которая, по-видимому, затрагивает почти 50% населения планеты. Маленькие дети подвергаются повышенному риску дефицита цинка из-за относительно высокой потребности в нем для обеспечения роста и развития организма. Риск особенно высок среди бедных, чье питание характеризуется низким содержанием мяса и состоит в основном из продуктов растительного происхождения, богатых плохо усваиваемым цинком, связанным растительными лигандами, такими, как фитат и некоторые типы волокон. Потенциальным решением этой проблемы является обогащение специальных пищевых продуктов, например выпечки, цинком и смесью других микронутриентов, которые способствуют метаболизму цинка. Здесь мы описываем один из таких продуктов и предлагаем возможный протокол испытания для оценки эффективности его применения для детей и других групп риска.

BACKGROUND

The problem of diets low in bioavailable zinc is an old one. As noted by Solomons (2001),«At no time during the last 400 generations, i.e., through the agricultural era, has either the intake of zinc or its bioavailability been as high as it was for the 10,000 generations that preceded it.»

Zinc deficiency, estimated prevalence nearly 50% (Brown, Wuehler et al., 2001), is a highly important cause of human morbidity. Macro-causes of zinc deficiency include economic status, availability of food, personal choices, food chemistry, and subject chemistry and physiology. Consumers with limited economic resources may subsist a narrow variety of foods derived mainly from plants, and thus are at high risk of zinc deficiency (Sandstead, 2000; Hunt, 2003). When income is not the primary factor influencing food selection, choice has a greater influence on zinc nutriture and the status of all other micronutrients. These conditions occur in the context of the level of adequacy of other nutrients in

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the diet. Increased risk of zinc deficiency in communities is suggested by food frequency histories that indicate infrequent consumption of foods rich in bioavailable zinc, in contrast to frequent consumption of foods rich in indigestible zinc binding ligands. Diseases that increase loss of zinc or reduce zinc absorption suggest individuals at high risk of zinc deficiency, especially when dietary sources of zinc are limited.

Zinc from animal flesh is highly bioavailable (Gallaher et al. 1988; Hunt et al., 1995, 1998, 2008; Hunt, 2003) and red meat is the richest common source (Table 1). In contrast, plant flesh (other than seeds) is low in zinc and contains indigestible zinc binding dietary fiber ligands (Kelsay et al., 1979). Plant seeds are relatively rich in zinc, but are also rich in indigestible zinc binding ligands, such as phytate (Angel et al., 2002) and dietary fibers (Reinhold et al., 1976; Ismail-Beigi, Faraji et al., 1977; Ismail-Beigi, Reinhold et al., 1977). In addition, heating of foods causes condensation of sugars and amino acids to form Maillard browning products (Van Soest et al., 1991) that bind zinc.

Under optimal conditions of consumption of a wide variety of foods the likelihood of adequacy of all micronutrients is high (Nilson, Piza, 1998). Variety of foods is essential because nutrients are not distributed evenly among foods. Instead, certain foods are rich in some nutrients and not others. In the case of zinc, uneven distribution among foods is illustrated by Table 1. In the absence of a wide variety of foods, risk of micronutrient deficiencies increases, and multi-micronutrient deficiencies are far more likely than single deficiencies. Usually one micronutrient is more deficient than others, and is designated most limiting. In the past associated clinical signs were often attributed to that single deficiency. However, in truth, the other simultaneous deficiencies also cause clinical signs. For example, severe iron deficiency typically causes hypochromic microcytic anemia. Associated clinical signs in adolescents have included stunting and hypogonadism caused by zinc deficiency (Prasad et al., 1963; Sandstead et al., 1967). In addition, iron deficient individuals are sometimes also deficient in folate. Repletion of iron status is followed by macro-cytic anemia responsive to folate. Thus the clinical signs actually reflect simultaneous deficiencies; and treatment with only the most limiting nutrient is almost always less effective than simultaneous treatment with a broad mixture of other micronutrients, some of which are subclinically deficient. This phenomenon was recently measured by Allen (Allen et al., 2009) in children. They compared effects treatment with a multi-micronutrient preparation, placebo, single or two micronutrients on length, weight, concentrations of hemoglobin, zinc and retinol, and motor development. Multi-micronutrients were the most efficacious treatment.

Zinc deficiency has a wide clinical spectrum, of which only the most severe (and infrequently observed) is clinically obvious. For example, severely deficient patients may present with acrodermatitis (Arakawa et al., 1976; Kay et al., 1976), or severe stunting and hypogonadism (Prasad et al., 1963; Sandstead et al., 1967). A less obvious zinc deficiency is exempli-

Table 1. ***Zinc content of representative foods in the United States, per common measure (USDA, 2002)****

Zinc content	Foods
>15 mg	Oyster Peanut Butter Crunch ®* Product 19 ®* Total ®*
5—10 mg	Beef Lamb Duck King Crab Wheaties ®*
4—5 mg	Beef liver Beef Lamb Pork Capitan Crunch ®* Quaker Oats ®*
3—4 mg	Lamb Pork Veal Turkey dark meat Blue Crab Rice Chex ®* Corn Chex ®* Cheerios ®* Whole wheat flour*
2—3 mg	Lamb Pork Lobster Clam Yogurt Skim Milk White bean* Chick pea* Lentil* Corn meal*
1—2 mg	Pork loin Chicken dark meat Sword fish Shrimp Mushroom White wheat flour Navy bean* Black bean* Pinto bean* All Bran ®* Nuts*
<1 mg	Chicken breast Chicken liver Salmon Tuna Other Finfish Vegetables White rice Egg Tofu* Cheddar cheese Blue cheese Cottage cheese Nuts*

* Note that many cereal products, legumes and nuts are rich in indigestible zinc binding ligands such as phytate, certain dietary fibers, and/or products of non-enzymatic Maillard browning.

fied by patients with various types «non-specific» dermatitis, non-stunted children with low growth (Brown et al., 1998; Sandstead et al., 1998), children with suppressed neuropsychological functions (Sandstead et al., 1998), children with cell mediated immune deficiency (Sandstead et al., 2008) and infants, children and others with infections (Walker, Black, 2004), women with pre-pregnancy diets rich in plant proteins and indigestible zinc binding ligands, that are low in animal protein and zinc, who are thus at increased risk of delivering infants with neural tube defects (Velie et al., 1999), women whose diets are insufficient in zinc during pregnancy and thus are at increased risk of premature delivery and small infants (Scholl et al., 1993). Zinc deficiency is least likely to be detected in subjects with no complaints such as was the case in low-income pregnant women with normal weight and appearance and no clinical complaints who were recruited into a randomized controlled trial of zinc and micronutrients simply because their plasma zinc concentrations were below the obstetric clinic average. The investigators were surprised when maternal treatment with zinc and micronutrients from the 19th week of gestation increased birth weight 450 g more than in controls whose mothers were treated with zinc alone (Goldenberg et al., 1995). Another example is healthy appearing young women who choose to eat little if any red meat. As a consequence they are at increased risk of iron deficiency without anemia and zinc deficiency manifest by low tissue rapidly exchange able zinc (Yokoi et al., 2007) associated with an increased likelihood of abnormal cognition (Penland et al., 2002). Such individuals appear normal, while at the same time they are functionally abnormal. A third example is apparently healthy low income children who showed significant increases in lean-body mass when treated with zinc and micronutrients as contrasted to children treated with micronutrients alone (Egger et al., 1999).

Zinc's essentiality is related to its chemistry. Zinc is a stable divalent cation with an ionic radius that facilitates coordination chemistry (Chesters, 1989). Zinc is atransition element that does not directly participate in oxidation or reduction. Thus zinc is ideal for affecting structure and function of many proteins. About 10% of the human genome encodes proteins with motifs suitable for zinc binding (Andreini et al., 2006). Included are 933 enzymes of all categories, 957 transcription factors, 221 signaling proteins, 141 transport/storage proteins, 53 proteins with structural metal sites, 19 proteins involved in DNA repair, replication and translation, 427 zinc finger proteins, 456 other zinc proteins of unknown function. Zinc is also essential for protein folding (Maret, Li, 2009). Zinc functions, as do all nutrients, in the context of interdependence with other micronutrients. Optimal function requires that all micronutrients are present in appropriate amounts. An example of zinc acting in concert with other micronutrients to produce an essential outcome is zinc's several roles in the methionine cycle/transsulfuration pathway that also requires folate, riboflavin, pyridoxine, cobalamine, choline/betaine and methionine for production of S-adenosyl-methionine (Maret, Sandstead, 2008).

Our experience with treatment of zinc deficiency provided evidence that zinc treatment is most efficacious when other micronutrients are also adequate. The relative responses were evident in a double blind randomized controlled treatment trial in 740 Chinese children one third of which were respectively from Chonqing, Qingdao or Shanghai. Children from Shanghai had the highest mean zinc concentrations and did not respond to treatments as far as growth was concerned. Growth of children from the other cities was responsive to the treatments: zinc alone, zinc with other micronutrients and other micronutrients alone. Zinc with other micronutrients was the most efficacious for growth while other micronutrients alone were usually superior to zinc alone. In all locations neuropsychological function were affected by treatments. Zinc with other micronutrients was significantly more efficacious for eye-hand coordination and recognition of oddity. For these tasks responses to zinc alone or micronutrients alone were similar (Sandstead et al., 1998). Other experiments in Mexican-American children (Sandstead et al., 2008) and in women (Penland et al., 2002) that did not include a zinc only group, also showed zinc with other micronutrients more efficacious then micronutrients alone. Consistent with these observations researchers in Thailand showed that fortification of seasoning powder fortified with zinc, iron, iodine and retinol found improved immunity, and cognition of children over a period of 31 weeks (Manger et al., 2008).

In our opinion, populations at greatest risk of zinc deficiency are low-income children (Sandstead et al., 2008), young women of child bearing age (Yokoi et al., 2007), pregnant women (and fetus) (Goldenberg et al., 1995) and the elderly (Sandstead et al., 1982).

We suggest that such populations will benefit from participation in randomized controlled trials designed test our hypothesis that cookies (or other culturally acceptable special foods) fortified with zinc and a broad mixture of micronutrients similar in principle to the mixture we administered to subjects in previous research, will be more efficacious for zinc requiring functional outcomes than cookies fortified with zinc alone or other micronutrients alone.

Preparation of effective fortified cookies will require that micronutrients at risk of peroxidation are protected. This will be accomplished through microencapsulation of such micronutrients using «fluidized bed coating» (air suspension coating) that is commonly used to produce products for incorporation into baked goods (Wilson, Shah, 2007). Solid particles of the core material (individual vitamins and minerals) are suspended in an upward moving column of air that may be heated or cooled. When the particles reach the necessary level in the column at an appropriate temperature, they are sprayed from above with atomized particles of the coating material to form an impermeable but digestible coating. The coating may be applied molten or dissolved in a solvent. The molten coat solidifies in cool air, while the solvent-based coat hardens as solvent evaporates (Risch, Reineccius, 1995). Particles are passed through

the air stream many times to cover them completely. Optimal encapsulation is likely to be achieved when core particles are 50 and 500 microns in diameter (Gibbs et al., 1999). Critical factors affecting the quality of the product are the volume of fluidized air suspending particles in the air stream, the duration of the surface coating time, and the temperature of the air (Risch, Reineccius, 1995). The various coating materials include cellulose derivatives, dextrins, emulsifiers, lipids, protein derivatives and starch derivatives (Shahidi, Han, 1993).

The following guidelines have been proposed to facilitate the efficacy of fortified foods (Nilson, Piza, 1998).

• The food must be culturally acceptable and frequently consumed.

• Food consumption should be uniform and range predictable.

• The fortifying nutrients should relate to need.

• The fortifying nutrients should be efficacious when food is eaten as usual.

• Fortifying nutrients should be compatible with other nutrients.

• Fortifying nutrients should be stable under usual conditions.

• Fortifying nutrients should be physiologically available.

• Fortifying nutrients should not impair color, taste, smell, texture, cooking properties, or shelf-life.

• Technical facilities must be adequate for continuous production.

• Quality control must be a continuous process.

• Cost must be affordable for consumers.

Cookies will be prepared by a commercial bakery using the following recipe: 1 cup butter, 1 cup shortening, 2 cups sugar, 3 eggs, 6 cups flour, 3 tsp baking powder, 1 tsp salt, 3 tsp vanilla. Cream butter, shortening and sugar; add eggs and vanilla; divide the dough into two equal batches. Based on the number of cookies in the batch the appropriate amount of micronutrient premix (Table 2) will be added so that each cookie contains the specified amount of the micronutrients. Bake at 350 °F (ca. 177 °C) for 16 minutes.

Table 2. ***Composition of 290 mg of the premix, without zinc, for young children, 4—8 years of age (Minimum)***[1–7]

Ingredient	Quantity
Vitamin A (Retinol Acetate, USP-FCC)	1665 IU
Vitamin D_3 (Cholecalciferol, USP)	600 IU
Vitamin E (d-alpha-Tocopherol Acetate, USP-FCC)	12 IU
Vitamin K_1 (Phytonadione, USP)	90 mcg
Biotin (USP)	30 mcg
Pantothenic acid (D-Calcium Pantothenate, USP)*	5 mg
Vitamin B_1 (Thiamin Mononitrate, USP)*	1 mg
Vitamin B_2 (Riboflavin, USP)*	1.1 mg
Niacin (Niacinamide)*	11 mg
Vitamin B_6 (Pyridoxine HCl, USP)*	1.3 mg
Vitamin B_{12} (Cyancobalamin, USP)	2 mcg
Chromium (Chromium yeast)	30 mcg
Copper (Copper Gluconate, USP)*	1.0 mg
Iodine (Potassium Iodide, USP-FCC)	95 mcg
Manganese (Manganese Citrate, FCC)	1.8 mg
Molybdenum (Molybdenum Amino Acid Chelate)	34 mcg
Selenium (Selenium Yeast)	45 mcg
Maltodextrin (Maltrin M-100, FCC)	QS

* signifies microencapsulation;
USP — U.S. Pharmacopeia;
FCC — Food Chemicals Codex

Notes:

[1] By Fortitech, Riverside Technology Park, 2105 Technology Drive, Schenectady, NY 12308.

[2] Microbial testing includes total plate count, E. coli (MPN), and Salmonella.

[3] Certificate of analysis. Each batch is furnished with complete Certificate of Analysis.

[4] Shelf life of at least 6 months under conditions of dry ventilation, tightly closed, original containers, no exposure to direct sunlight or excessive heat.

[5] Usage rate, 290 mg per serving, for premix without zinc.

[6] Usage rate, 302 mg per serving, for premix with 12 mg zinc (as zinc sulfate, USP-FCC). This amount of zinc is equivalent to 3 x the estimate average requirement (EAR) of 4 mg for 4—8 year old children (Otten et al., 2006). This amount of zinc should be satisfactory for children whose diets contain moderate levels of phytate. Higher amounts of zinc will be necessary when anticipated intakes of phytate are high (Hunt et al., 2008; Hunt, Beiseigel, 2009; Hambidge et al., 2010), or if efficacy of zinc is found to be limited.

[7] Amounts of micronutrients are equivalent to 1 EAR or Adequate Intake (Otten et al., 2006), except:

[a] For projects on populations where relatively severe multi-micronutrient deficiencies are likely, the dose of specific other micronutrients of special concern (a judgment call) is increased to at least 2 EARs.

[b] For projects in the USA folic acid is excluded because cereal products in the USA are fortified with folic acid.

[c] Because iron can suppress zinc absorption, iron is excluded, except when serum ferritin is less than 20 mg/L, then we suggest 1 EAR of iron is included.

[d] Ascorbic acid is excluded because unconfirmed studies suggest it can interfere with zinc absorption (Kies et al., 1983). If food frequency histories suggest low ascorbic acid consumption is likely subjects will be supplemented separately with ascorbic acid.

[e] Copper is added at 1.0 mg because of evidence in humans that zinc treatment can impair copper nutriture (Sandstead, 1995).

PLAN FOR TESTING ZINC AND MICRONUTRIENT FORTIFIED COOKIES

Experiments in children might include 4 treatment groups: 1) cookies fortified with zinc and other micronutrients, 2) other micronutrients alone, 3) zinc alone, and 4) cookies without fortification. Treatments will be administered daily. After 10 weeks, all subjects not given cookies fortified with zinc and micronutrients will be switched to cookies fortified with zinc and micronutrients, and all subjects will be treated an additional 10 weeks. The 10 weeks of treatment is based on our previous research (Sandstead et al., 1998, 2008). We anticipate that the period of treatment will be modified in later experiments based on longitudinal observations in early studies. The cross over assures that all subjects benefit from the most optimal treatment. Serial observations of outcomes will identify peak response. The data will allow development of improved designs for assessing response.

Outcomes measurements at baseline and follow-up should be minimally invasive. Potential examples are:

1. Qualitative/quantitative (on subgroup) food frequency and energy consumption.

2. Indices of zinc status, e.g., plasma, granulocyte, lymphocyte, and hair zinc. Plasma and hair zinc are insensitive. Granulocyte and lymphocyte zinc are highly sensitive but are difficult to measure at this time.

3. Change in length of lower leg by a highly sensitive digitized devise that measures length of lower leg from bottom of heel to top of knee (Cronk et al., 1989; Stallings, Cronk, 1993; Sandstead et al., 1998).

4. Change in lean mass by bioelectrical impedance (Ellis, 2000; Bray et al., 2002; VanderJagt et al., 2002; Diaz-Gomez et al., 2003; Rush et al., 2003; Sun et al., 2003; Marreiro et al., 2004).

5. Height by stadiometer.

6. Weight by beam balance

7. Serum anti-inflammatory cytokines (Sandstead et al., 2008).

8. Ratio of CD4 to CD8 T-cells

9. CD73 T-cells (Beck et al., 1997).

10. Serum indices of peroxidation (malondialdehyde) and inflammation (C-reactive protein) (Bao et al., 2010).

Sample size calculations need to be done to assure adequate sample size for specific tests. For example 100 subjects per group might be required for indices of growth (Sandstead et al., 1998). On the other hand experience suggests 25 per group might be adequate for indices of immune response and inflammation (Sandstead et al., 2008).

It is important that progress is evaluated periodically by a independent reviewers, and the study stopped when sufficient data are collected.

Costs will depend on many factors.

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