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Epidemiology of Micronutrient Deficiencies in Developing and Developed Countries, Specifically Zinc, Copper, Selenium and Iodine

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Micronutrient Deficiencies around the World

Trace mineral deficiencies in humans were first studied in relation to iodine deficiency and thyroid function, and iron deficiency and anemia. Zinc, copper and selenium deficiencies have become a matter of concern only over the last 40 years. Micronutrient deficiencies are frequently found to be combined in the same communities, especially in those less privileged. The effects of micronutrient deficiencies on population health have received great attention in the last years in studies dealing with the burden of disease [1, 2]. The World Health Organization has proposed epidemiological screening for populations at risk of disease based on suspected micronutrient deficiencies and on indices linked to long-term ill health [1]. An approach to defining the level of population risk based on subclinical signs of micronutrient deficiencies has been proposed taking into account: seasonal weight loss; women's low body mass index; low birth weight; rate of stunted children, and iodine, vitamin A and iron deficiencies (table 1). Recent studies on the burden of disease have also included zinc deficiency [2, 3].

Zinc Deficiency

One of the main constraints to determining the prevalence of zinc deficiency in population groups around the world is the lack of reliable biomarkers. Despite the large number of zinc status indices proposed, none of them present high

Table 1. An approach to defining the level of population risk based on subclinical signs of micronutrient deficiencies

	IV (severe prevalence)	III (moderate to severe)	II (mild and widespread)	I (mild and clustered)
Seasonal weight loss	>3	≥2 to <3	≥1 to <2	<0.5
Women's low body mass index	≥40	≥30 to <40	≥20 to <30	≥10 to <20
Low birth weight	≥25	≥10 to <25	≥5 to <10	<5
Stunted children	≥40	≥20 to <40	≥10 to <20	<10
Iodine deficiency	>99	≥50 to <99	≥20 to <50	<20
Vitamin A deficiency	≥20	≥10 to <20	≥2 to <10	<2
Iron deficiency	≥80	≥50 to <80	≥30 to <50	<12

From the Commission on the Nutritional Challenges of the 21st Century [1].

sensitivity and specificity to detect subnormal degrees of zinc status, especially mild and moderate. Instead, severe zinc deficiency shows markedly decreased zinc tissue concentrations. Thus, the diagnosis of zinc deficiency has frequently been based on clinical signs suggestive of zinc deficiency and a positive response to zinc supplementation in some biological functions. Currently, a suitable, although still imperfect, approach to screening for zinc deficiency is the assessment of the adequacy of zinc intake, which can be complemented by plasma zinc levels [4]. In addition, a post-intervention positive effect on some zinc-related clinical variables provides supportive evidence to characterize the community studied in terms of its zinc levels.

Dietary zinc adequacy is related to the total zinc content of food and zinc bioavailability. One of the most important dietary factors that reduce intestinal zinc absorption is phytic acid. It has been estimated that a phytate:zinc ratio of >15 significantly decreases zinc absorption, thus increasing the zinc needed to be provided by the diet. Most of the developing world presents phytate:zinc ratios above this cutoff point (e.g., Sub-Saharan Africa 26.9, South Asia 26.9, Latin America 21.1). Instead, the developed world has ratios well below that cutoff point [4].

With the exception of women of childbearing age, in which menstrual losses are the main determinant of iron status, the prevalence of zinc deficiency is probably similar to that of nutritional iron deficiency in all other age groups. In these, the characteristics of the diet are the key factors. Dietary patterns high in unrefined grains and fiber and low in animal protein, especially meat, induce a high risk of both iron and zinc deficiencies. Iron deficiency anemia has been estimated to have a low prevalence in Europe, medium prevalence in the Americas (14% as a whole), and high prevalence in the South-East Asian, African, East Mediterranean and West Pacific areas (29–39%) [5].

Probability estimates for the risk of zinc deficiency can be calculated from dietary data alone. Diets with a proportion of animal protein between 10 and 25% are adequate to support zinc nutrition [6]. However, to determine the severity of zinc inadequacies, dietary information must be analyzed along with biochemical and functional indices. Since zinc-rich foods are mainly animal products, it is possible to estimate a higher risk of zinc deficiency in regions where the consumption of livestock products is low. Estimates based on the production, import and export of these foods by countries and regions show a very low consumption in South Asia and Sub-Saharan Africa [7].

Zinc deficiency has been included as a related exposure variable for risk of disease in populations (defined as less than the US recommended dietary allowances for zinc, and with a theoretical minimum intake established as the entire population consuming sufficient dietary zinc to meet the physiological needs, taking into account routine and illness-related losses and bioavailability). The outcomes associated with zinc deficiency are diarrhea, pneumonia and malaria in children aged <5 years. In the 2002 report by the WHO [3], analysis of the disabilities-adjusted life years (DALYs) associated with zinc deficiency estimated 11–18% DALYs for diarrheal disease, 19% for lower respiratory disease and 18–19% for malaria in developing countries with high mortality; 3–5% for the same diseases in developing countries with low mortality, and 1–3% in developed countries [2, 3] (table 2). In total 800,000 deaths worldwide were attributable to zinc deficiency, 1.4% in males and 1.5% in females.

Zinc Deficiency in Developing Countries

The main conditions accompanying zinc deficiency in developing countries are: low consumption of meat or fish along with increased phytate and fiber consumption; protein-energy malnutrition; infectious diseases, particularly acute diarrhea and malaria, and fetal growth retardation [4].

Protein-Energy Malnutrition

Protein-energy malnutrition is a condition associated with multiple macro- and micronutrient deficiencies, including zinc. Thus, in communities where this condition is prevalent, zinc deficiency is also present. Analysis of DALYs shows childhood and maternal undernutrition as the main isolated condition associated with burden of disease (140 million years). Over 16% DALYs have been estimated in Africa and South-East Asia [3]. According to the WHO, approximately 27% (168 million) of children under 5 years are underweight [8].

Zinc and Growth

There is consistent evidence on the relationship between zinc deficiency and postnatal growth retardation, including a recent refined meta-analysis [9] (fig. 1). The effect of zinc supplementation was greater in stunted children (height/age < -2 z score). Countries or communities with a stunting prevalence

Table 2. Selected population attributable risk factors (% DALYs for each cause)

	World	High mortality developing	Low mortality developing	Developed countries
Underweight				
Diarrheal disease	45	49	21	12
Low birth weight	10	12	3	3
Lower respiratory infection	40	46	25	8
Malaria	45	45	14	0
Measles	33	34	23	10
Protein-energy malnutrition	88	88	92	78
Iron deficiency				
Anemia	100	100	100	100
Maternal mortality	11	13	6	1
Perinatal mortality	19	22	13	2
Vitamin A deficiency				
Diarrheal disease	18	19	9	0
Malaria	16	17	7	0
Maternal mortality	10	12	5	0
Measles	15	15	13	0
Zinc deficiency				
Diarrheal disease	10	11	3	2
Lower respiratory infection	16	19	5	2
Malaria	18	18	3	1

From the WHO [3].

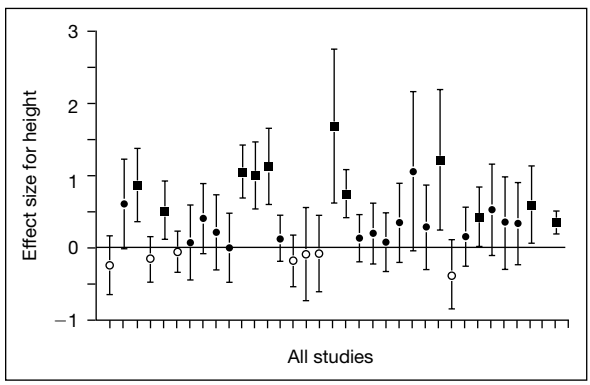

Fig. 1. Mean effect size and 95% CI for the effect of zinc supplementation on children's linear growth. Results of individual studies and a meta-analysis. Adapted from Brown et al. [9].

Table 3. Studies analyzing the effect of zinc supplementation during pregnancy on fetal growth (birth weight and prematurity) in humans

Citation	Country	Zinc mg	Controls	n	Birth weight	Prematurity
Hunt, 1984	USA	20	MVM	213	–	–
Hunt, 1985	USA	20	MVM	138	–	–
Ross, 1985	South Africa	30	Placebo	127	–	–
Kynast, 1986	Germany	20	No placebo	524	↑	–
Mahomed, 1989	UK	20	Placebo	494	–	–
Cherry	USA	30	Placebo	556	–	↓(multip.)
Simmer, 1991	UK	22.5	Placebo	56	↑	–
Garg, 1993	India	45	No placebo	168	↑	↓
Goldenberg, 1995	USA	25	MVM	580	↑	↓
Jonsson, 1996	Denmark	44	Placebo	1,206	–	–
Caulfield, 1999	Peru	15	Placebo	1,100	–	–
Osendarp, 2000	Bangladesh	30	Placebo	559	–	–
Castillo-Durán, 2001	Chile	20	Placebo	507	–	↓
Wieringa, 2001	Indonesia	30	β-carot.	228	± boys, Zn carotene	–

MVM = Multivitamin mineral supplement. From Castillo-Durán and Weisstaub [10].

of >20% are at high risk of associated micronutrient deficiencies, including zinc [1].

Low birth weight, as an index of fetal growth retardation, may also be associated with zinc deficiency. Nevertheless, evidence gathered to date [10–12] on the effect of zinc supplementation during pregnancy on birth weight has not confirmed this expectation (table 3). This issue is still being studied.

Zinc and Infections

There are several studies analyzing the magnitude of zinc intakes, but not many on zinc losses during infectious diseases. Zinc losses of >100 μg/kg/day as found in acute or protracted diarrhea may induce zinc deficiency, especially when associated with a decreased zinc intake [13]. Ruz and Solomons [14] showed that for each day of acute diarrhea, the increased loss of zinc duplicates the need for zinc. Studies on zinc supplementation in poor communities in India, Bangladesh and other countries have found decreased risks of acquiring infectious diarrhea, respiratory infections (pneumonia) or impetigo and sepsis [15–18] (table 4). Others have shown a decrease in the duration of diarrheal processes [16, 17]. Zinc supplementation, added to other micronutrients from 1 to 9 months of age, also decreased the mortality of small-for-gestational age infants (RR = 0.32; CI = 0.12−0.89) mainly by decreasing diarrhea and sepsis [17, 18]. Breast-feeding was also independently associated with lower mortality.

Table 4. Trials evaluating the preventive effects of zinc supplementation on prevention of diarrhea and pneumonia

Country	Author	Number of subjects	Age months	Other criteria	Diarrhea incidence	Pneumonia incidence
Vietnam	Ninh, 1996	146	4–36	W/A or W/L <-2 z score	44% lower	44% lower
India	Sazawal, 1997 Sazawal, 1998	579	6–35	Recovery from diarrhea	8% lower	43% lower
Mexico	Rosado, 1997	194	18–36	–	37% lower	–
Guatemala	Ruel, 1997	89	6–9	–	18% lower	–
Jamaica	Meeks-Gardner, 1998	61	6–24	W/A <-2 z score	8% lower	88% lower
Brazil	Lira, 1998	205	0–6	Low BW	28% lower	–
Peru	Penny, 1999	159	6–35	Recovered persistent diarrhea	12% lower	15% lower
Papua New Guinea	Shankar, 1999	274	6–60	–	12% lower	–
Burkina Faso	Muller, 2001	709	6–31	–	16% lower	–
India	Bhandari, 2002	2,482	6–30	–	–	26% lower

W/A = Weight-for-age; W/L = weight-for-length; BW = body weight. Adapted from Black [18].

In spite of some initial evidence suggesting a positive effect of zinc supplementation on the incidence of malaria in children, recent studies have failed to find such an effect [19, 20].

Zinc Deficiency in Developed Countries

These countries present, as a whole, a low risk of zinc deficiency. Nevertheless, there have been some reports suggesting zinc deficiency in some specific groups.

The classic studies by Walravens and Hambidge [21] in Denver, USA, showed a subnormal zinc status in a pediatric population from poor districts of Denver in the 1970s. Similar evidence was added later in other American and Canadian cities [22, 23]. In 1989 in pregnant African-American adolescents, Cherry et al. [24] found a decrease in the rate of low birth weight when zinc supplementation started before the 25th week of gestation in normal and overweight pregnant women. In the early 1990s in Paris, France, Walravens et al. [25] found an increased risk of zinc deficiency in infants of migrant African families who exclusively breast-fed their babies beyond 6 months of age. Zinc supplementation (5 mg/day) increased the length and weight of male infants, but not females. This practice of prolonged breast-feeding along with delayed introduction of complementary foods may be a risk factor for zinc deficiency in the second semester of life. Preliminary results of zinc

supplementation in Mexican-American children, 6–8 years old, from Brownsville, Tex., suggest that zinc deficiency may be prevalent in that community [26].

In summary, zinc deficiency is highly prevalent in developing countries, probably similar to iron deficiency. It is associated with low zinc diets, diets high in phytates and fiber, protein-energy malnutrition, diarrheal disease, and low birth weight. This condition affects most of the poor countries in South-East Asia and Africa, and also countries in the Middle East and Latin America. Zinc deficiency can also be found in specific groups in developed countries, especially among those migrating from less affluent communities.

Copper Deficiency

Copper deficiency was described in the 1960s in infants recovering from malnutrition and fed unfortified cow's milk. The effects of copper deficiency have been described: hematological signs such as neutropenia, leucopenia and anemia; immune compromise, and increased risk of infections. Growth delay and bone disease may also be other clinical signs. Protein-energy malnutrition and low birth weight appear as risk factors of copper deficiency, along with early weaning and feeding with unfortified cow's milk. A history of acute diarrheal episodes and the increased fecal loss of copper associated with it increase the risk of copper deficiency. The magnitude of copper deficiency has not been studied in large community settings. Because copper is widely distributed in foods and absorption is larger than other trace elements, it is not likely that apparently healthy individuals consuming mixed foods present with copper deficiency. Copper deficiency becomes an issue, particularly in children, under certain conditions in which some of the following factors interact: malnutrition; low copper recovery diets; prematurity, and diarrhea. The prevalence of copper deficiency here is unknown. Limited data in malnourished children indicate that up to 50–80% may have low plasma copper [27, 28].

Selenium Deficiency

Among the main determining factors of selenium status is selenium intake, rather than selenium absorption. Both organic and inorganic forms of selenium are absorbed at high rates, i.e. >70%. Likewise, selenite and selenate forms are absorbed at a similar rate (Van Dael, personal commun.). The selenium content of foods is strongly affected by soil characteristics. As a consequence, the selenium content of foods, especially those of vegetable origin, may vary over such a wide range that the use of food composition tables becomes meaningless. In general terms, the best sources of dietary

selenium are seafood and meats; grains are highly variable depending on soil conditions; fruits and vegetables do not contribute significantly to the total intake. Variations in selenium in soils and foods are important. They determinate that certain geographic locations around the world have been classified as areas of 'low' and 'high' selenium [29].

Current recommended selenium intakes are 20 μg/day for children 1–3 years old, 30 μg/day for those 4–8 years old, 40 μg/day for 9–13 years, and 55 μg/day 14 years old and beyond [30]. No differences have been established by gender. Excess selenium is toxic. Clinical symptoms of its toxicity include severe irritations of the respiratory system, metallic taste in mouth, signs of rhinitis, lung edema, and bronchopneumonia.

Studies Conducted in Developing Countries

Iyengar et al. [31] studied the dietary intake of essential minor and trace elements from Asian diets by analyzing about 700 diet samples. The average dietary selenium supply ranged from 52 to 141 μg/day. In Latin America, Venezuela has been the focus of attention due to the existence of areas with naturally high selenium in soils. Bratter et al. [32] measured a selected set of parameters of selenium, red blood cells, serum and hair of children, and breast milk from seleniferous areas of Venezuela. In these areas, selenium intakes can be ten times or more than that observed in areas considered as 'low selenium' such as Finland or New Zealand. Ruz et al. [33] studied the selenium distribution in Chile by using free-range hen's eggs as a selenium monitor. This was followed by direct dietary analysis and biochemical determinations (red blood cell count and serum glutathione peroxidase, serum selenium and toenail selenium) in adults living in three distinct cities. The mean selenium intake ranged from 52 to 99 μg/day. The first city was a cold and rainy midland location, whereas the third was a coastal town by the Atacama Desert [34]. A further study was conducted in schoolchildren in the city with the lowest selenium intake to investigate the potential association between iodine supplementation, selenium status and goiter prevalence. The children in this city, despite having a relatively greater iodine intake, tended to have a higher goiter prevalence and, concomitantly, a lower selenium status [35].

The relationships between selenium and iodine metabolism have been a matter of concern in a number of studies in animals and humans. Vanderpas et al. [36] suggested that the high frequency of myxedematous cretins observed in certain areas of Zaire may result from a combined severe deficiency of both iodine and selenium. In 7- to 12-year-old Turkish children, Aydin et al. [37] attributed the high goiter prevalence to iodine and selenium deficiency. Untoro et al. [38] suggested that low environmental selenium availability may be an additional determinant for goiter in East Java, Indonesia. Zimmermann et al. [39], studying children from rural villages in the western Ivory Coast, concluded that although more severe selenium deficiency partially blunts the

thyroid response to iodine supplementation, oral iodized oil is an effective method for iodine repletion in goitrous children who are selenium-deficient. Correction of selenium status without a previous restoration of iodine status can worsen the altered thyroid metabolism [40].

Ahmed et al. [41] found indications of low selenium status in Sudanese children with marasmic-kwashiorkor. Subotzky et al. [42] studied children with kwashiorkor during the first 30 days of recovery. After this period a full clinical recovery was reached, with normalization of the plasma levels of selected trace elements, with the exception of zinc and selenium, indicating that this period of time may not be sufficient to allow a full recovery with respect to these two micronutrients.

Studies in Developed Countries

A number of studies have been carried out in Eastern Europe. A common feature has been the finding of rather low selenium intakes. Zachara and Pilecki [43] studied the daily selenium intake of breast-fed infants and the selenium concentration in the milk of lactating women in western Poland. The calculated mean daily selenium intake by breast-fed infants was 7.71 (range 3.67–17.17) μg/day. The selenium concentration in human milk in the region studied was uniform, but the daily selenium intake of breast-fed infants was lower than the recommended daily requirement. The authors attributed this to the low selenium content of the soil and consequently of the foodstuffs from this region [43]. Wasowicz et al. [44], also in Poland, reported average selenium intakes in children and adults of 30–40 μg/day. In Slovakia, Kadrabova et al. [45] found that the daily dietary selenium intake was 43.3 μg/day for men and 32.6 μg/day for women. In 1992 in the former Yugoslavia, Beker et al. [46] studied the selenium status of 8- to 15-year-old individuals of both sexes and from four distinct geographic locations by analyzing serum samples. The authors reported significant differences regarding age and sex but not by location; the mean serum selenium was 57 μg/l [46].

In Nordic Europe, Samuelson [47] studied the dietary intakes of vitamins and minerals in adolescents from Denmark, Finland, Norway and Sweden. Dietary calcium intake was high, whereas the intake of fiber, vitamin D, zinc and selenium and, in girls, iron were below the Nordic recommendations.

As a consequence of the naturally low selenium in Finnish soil, the addition of selenium to fertilizers began in the early 1980s. Kantola et al. [48] determined the impact of soil selenium supplementation over a 10-year period. selenium intake rose from 30–40 to 85 μg/day.

Recently, data on the dramatic decline of selenium intakes in the UK over the past 20–25 years have become available. In 1974 the reported selenium intake was 60 μg/day, whereas the current figure is as low as 30–40 μg/day. Although no functional consequences have been recognized, the significance of the biochemical changes observed in UK individuals supplemented with selenium is under study [49].

Table 5. Current magnitude of iodine deficiency disorders by goiter by WHO Region (1999)

	Population in millions	Population affected by goiter	
		in millions	% of the region
Africa	612	124	20
The Americas	788	39	5
South-East Asia	1,477	172	12
Europe	869	130	15
East Mediterranean	473	152	32
Western Pacific	1,639	124	8
Total	5,858	741	13

From WHO-UNU and the International Council for Control of Iodine Deficiency Disorders [50].

Iodine Deficiency

The most common indicators used to assess iodine status are urinary iodine, as determined in a casual urine sample, and thyroid volume, as measured by ultrasonography. Evaluations of iodine deficiency throughout the world by the WHO show differences in the various regions, with the highest prevalence of iodine deficiency in East Mediterranean countries and Africa. The iodine deficiency disorders (IDDs) prey upon poor, pregnant women and preschool children, posing serious public health problems in 130 developing countries. IDDs affect over 740 million people, 13% of the world's population, and 30% of the remainder are at risk. It has been estimated that nearly 50 million people suffer from some degree of IDD-related brain damage [50]. Associated with salt iodinization, the prevalence of goiter has decreased in the Americas to <5% (table 5).

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Discussion

Dr. Vasquez-Garibay: Do you think that pneumonia is a good indicator of infections in zinc deficiency because only a few studies have found some results?

Dr. Castillo-Durán: At this time all the studies on the association between zinc deficiency and pneumonia are related to very severe zinc deficiency in countries like India, Bangladesh, and Indonesia where severe deficiency is prevalent. Some studies have well demonstrated an effect of zinc deficiency on immunity, mainly cellular immunity, and there are some studies showing an association with IgA deficiency. There are several studies at this time that also demonstrate the effect well.

I don't know if this effect is also prevalent in countries where marginal zinc deficiency is prevalent.

Dr. Guesry: What type of criteria would you recommend to define zinc deficiency? We know that plasma zinc is not a good indicator, particularly during infection when there is sequestration of zinc in other pools.

Dr. Castillo-Durán: There is a lot of discussion at this time. Several studies propose that plasma zinc with a cutoff close to 80 μg/dl or 12.3 μmol/l may be one of the markers for analyzing the prevalence. Brown et al. [1] have used another approach which is to add the prevalence of low absorbable zinc associated with phytate intake to this factor; the molar ratio of >15:1 between phytate and zinc could possibly be associated with a high prevalence of zinc deficiency or high/low zinc absorption. At this time we need more information but we must use the information available. Plasma zinc is useful. Another measurement which is very difficult to use is white blood cell content. If red cells are used, then another measurement is needed because red cells are very difficult to use in community populations. At this time, the clinical effects, growth and infections are good markers for the suspicion of zinc deficiency, but we cannot say what the prevalence is because we have no reliable markers. For iron deficiency, it is 40–50%, but for zinc we suspect that it is similar to iron, but we cannot say if it is the same rate as iron or another nutrient.

Mr. Parvanta: Following up on this discussion of the indicator. For example, you mentioned that in some countries foodstuffs are being fortified with zinc. Do you think it is possible to use a marker like serum zinc as a way to track the potential impact of that fortification program rather than being concerned about what the deficiency is? Basically, in a way, it is more like looking at whether the intervention has actually been effective.

Dr. Castillo-Durán: Perhaps I can give you an example of fortification in my country. We have a cow's milk powder which is fortified with iron 10 mg/l, zinc 5 mg/l, copper 0.5 mg/l. Two years after it was introduced in Chile iron deficiency decreased from 30 to 10 or 8%. We analyzed the rate of low plasma zinc. At that time, when the program was beginning, we had about 40%, and presently we have 30% in 18-month-old children. What is the explanation? Can we say that 5 mgZn/l is not enough to produce a favorable response in low plasma zinc, or is there a negative interaction between the 10 mgFe/l and the 5 mgZn/l for this result in plasma zinc? In spite of this effect, growth increased during the last years and these children have improved from −1 to −0.3 length-for age z-score. This is only an example, I cannot give you the exact answer and we need more studies.

The erythrocyte zinc content has been analyzed in many studies. With experimental zinc deficiency it was demonstrated that the zinc content in the membrane could be a useful marker for zinc deficiency. But we did a study in our community and after some months could not find any effect of zinc supplementation on the content of red blood cell membranes. I think it is very difficult to use this marker for communities.

Dr. Gia-Khanh: I would like to ask about the interaction between iron and zinc. In a community of children we had 3 groups: 1 receiving iron only, 1 receiving zinc only, and 1 receiving iron and zinc, and the results were very clearly different between the 3 groups. In the group receiving iron, anemia is clearly decreased. In the group receiving zinc, diarrhea and pneumonia clearly increased. But in the group receiving iron and zinc supplementation, the results are not as clearly different. Is there an interaction between zinc and iron when they are given to children from 6 to 12 months?

Dr. Castillo-Durán: I think Dr. Lozoff will analyze the interaction between zinc and iron, or Dr. Lönnerdal in the next presentation.

Dr. Zlotkin: Just sort of focusing on epidemiology. It has been my observation that most of us talk in terms of prevalence in developed countries and prevalence in developing countries, as your slides demonstrated. Yet it is quite clear to me, in Canada

for example, that there are pockets of individuals within our developed country where micronutrient deficiency is in fact a significant problem. In Canada among our aboriginal populations, the prevalence of a micronutrient deficiency, like iron deficiency, may be as high as 40%. Yet if you look at national prevalence the number might be as low as 5–7%. In the developing world, and Mexico may be a good example where there is a burgeoning middle class, is it still fair for us to lump our prevalence data on the entire developing country, or in fact, as we sit here, is there a change going on where the 15 or 20% of the population who are becoming middle class are no longer at risk of micronutrient deficiencies. In fact if our national prevalence is 40% it means that in certain pockets it may be as high as 60 or 70%, whereas in other pockets it is as low as 5 or 10%. Should we be splitting rather than mounting at this point?

Dr. Castillo-Durán: We need more information from developing countries because, as you said, there are many pockets. In some countries these pockets are increasing because migration is increasing, and zinc deficiency is suspected in this kind of community. It would be an advantage if we could study these groups which may present with isolated deficiencies. This would allow us to analyze zinc deficiency or to control for a few other deficiencies. The problem in underprivileged communities in developing countries is that there are many deficiencies such as protein energy, many micronutrient deficiencies such as iron, copper, vitamin A, iodine, and many diseases. Fortification or supplementation can be tried but, in Guatemala or other countries, if the children present with acute diarrhea and environmental enteropathy, it is sometimes difficult to demonstrate very positive effects. In the future we may be able to compare these isolated deficiencies in developed countries with those mild deficiencies in developing countries.

Dr. Hurrell: I would like to question the assumption that zinc deficiency or the prevalence of zinc deficiency is as high as iron deficiency. My thoughts would be that phytic acid, which is often given as the reason, is much less inhibitory to zinc that it is to iron, and that most of the zinc studies have been in adults and not in children. Those that have been made in children, at least one of those studies, showed no effect of phytic acid on zinc absorption [2], and studies in infants are also nonexistent. The other reason would be that one of the main risk factors for iron deficiency is blood loss, which is not really a risk factor for zinc deficiency. Would you like to make some comments?

Dr. Castillo-Durán: I agree with you that we cannot use iron deficiency to define the suspicion of zinc deficiency, but there are some common effects. If we say that a low zinc intake is one of the risk factors, the same products in complementary foods contain iron and zinc. Another common factor is low birth weight related to low zinc and iron stores, which has been found to be common. As you said, it is not common that phytic acid is more related or more demonstrated for zinc status, but we need more information about the amount of phytate intake in children during complementary feeding after 6 months or between 6 months to 2 years old. It is different with the information related to blood loss, intestinal loss, which is more related to iron deficiency than to zinc deficiency. In the future we will be able to control for these confounding factors and analyze them. If we control these factors we can demonstrate some common effect of low zinc intake related to high zinc intake.

Dr. Gebre-Medhin: This is more a comment rather than a question, and I would like to reinforce what Dr. Guesry and Mr. Parvanta as well as Dr. Zlotkin have mentioned, and that is that these individual nutrients rarely occur without being associated with two fundamental things, protein energy malnutrition and infection. As long as this issue of criteria markers and indicators for pure authentic individual iron deficiency is not rushed, we will be in great trouble. Dr. Lönnerdal will go into basic issues on interrelations and interactions using experimental situations, but in humans it is getting more and more frustrating. The other comment I have is that if you give an

individual any nutrient you are likely to increase the serum level, and this has been known for perhaps 100 years. Anything that is given to anybody will usually increase the serum level. The other thing is that it will be compromised by protein energy status and infection. Now as long as these issues are not rushed, we will continue to be in trouble.

Dr. Neufeld: I just want to come back to Dr. Zlotkin's comment about the distribution of deficiencies in a country. We have recently conducted a nationally representative nutrition survey and found quite large differences for some micronutrients and for some nutritional problems within Mexico and less for other problems. For example iron deficiency anemia occurs all over Mexico, whereas with zinc deficiency there were differences, vitamin A, etc. I think it is very important to make sure that we look out for those differences in terms of monitoring progress and also in defining programs, something we need to focus on more.

Mr. Parvanta: I wonder whether you have some comments on indicators for diagnosing individuals versus diagnosing or assessing populations? I also wonder whether an indicator may be more applicable to a population assessment rather than in individually diagnosed subclinical cases or individual patients? I wonder whether there might be some way to assess populations using certain indicators that may not be as regressive to monitoring or assessing or diagnosing an individual, and specifically with zinc? Do you have any comment on that?

Dr. Castillo-Durán: For a good analysis it is sometimes difficult to find children without infection, in good condition and fasting. At this time, for individuals, when we get a good sample for zinc with no infection, we can say that it is a reliable marker if there is some information on plasma zinc under 80 μg/dl. Also if the history of these children presents other suspicious risk factors, for instance in the first years of life or repeated infections, then we can only suspect zinc deficiency. The purpose is to supplement and to demonstrate an effect. Similar to vitamin A, there are some studies that are trying to find out if there is some effect after zinc supplementation on plasma zinc, but there is no indication that the change is a good indicator for zinc deficiency. If we have 80 μg and we supplement this and increase to 90, the change is an indicator of zinc deficiency. At present we can only use the information available. For individuals plasma zinc is the only measurement associated with history. For communities we must analyze the problem. At this time there is a very high risk for very underprivileged communities. The problem at this time is to demonstrate whether marginal zinc deficiency is associated with some clinical effects, growth and infection. If an association is found, even at a marginal level, we can advance in this definition.

Dr. Gibson: New Zealand has just completed a national survey examining plasma zinc levels in children between 5 and 14 years of age. We are actually analyzing these data and I certainly believe, at the population level, that serum zinc can tell you very useful things about the distribution of zinc status in a population. It appears, with our New Zealand data, that the low zinc status is restricted to certain ethnic groups [3].

Dr. Cozzolino: We have been working with zinc and selenium in Brazil for a long time. I think at the moment the major problem is to discover a biomarker that will be useful to say that a patient is deficient or not, because plasma is always alright, the level is normal, but sometimes the patient has a deficiency. Do you think we need another biomarker to really tell us whether there is a deficiency or not, also with selenium? In Brazil we have found different levels of selenium, and we are trying to discover more about this mineral in Brazil. I think it is also important to know what biomarker is useful in this case. What do you think about the biomarkers?

Dr. Castillo-Durán: I agree with you. New information is appearing all the time proposing new biomarkers for selenium, for zinc and trying to demonstrate efficiency. Biomarkers are needed which are easy to perform and analyze in a population. There are some reliable markers but they are too difficult or too expensive to use. They are

not useful for us. If we can perhaps demonstrate that the changing zinc pool is useful to measure marginal zinc deficiency that would be very nice, but it is not available for individuals because it is too expensive. For selenium we might analyze glutathione peroxidase for zinc and selenium content in some tissues. But at this time we must also demonstrate what the selenium outcome is. Is the outcome perhaps an iron deficiency disorder because we have no other clinical outcome at this time? In the case of selenium we need much more metabolic information to advance to the communities, and we also need new information for zinc.

Dr. Yin: I would like to make some comments about selenium. As you know, China was probably a good example for selenium deficiency in the past. About 30 years ago, we had a long belt area from north-eastern to south-western China with a population of 200 million, in which there was a high incidence of Keshan disease and also Kaschin-Beck's disease. After selenium supplementation, the prevalence of the two diseases was significantly decreased. In the last 20 years, the prevalence and the great extent of these diseases have been alleviated along with improvements in the socioeconomic and living standards and nutritional status. In recent years in some low-selenium areas, although there was no selenium supplementation, the incidence of Keshan disease and Kaschin-Beck's disease has decreased. From this I think the general nutritional status should be considered, and if we improve the general nutritional status we can also decrease some micronutrient deficiencies.

Dr. Gibson: I would like to comment on the collection of blood samples for plasma serum zinc. When we were setting up the protocol for the national children's nutrition survey in New Zealand, we actually did a lot of work trying to establish standardized methods. One of the things I would like to just emphasize is that if you don't refrigerate the blood samples or store them on ice immediately after collection [4], and also separate the serum/plasma within a certain short space of time (i.e. within 2 h), you will find that your plasma or serum zinc levels do go up; during clotting, zinc may be released from platelets [5]. I think this is one of the reasons why we have such difficulty in interpreting so much of the data in the literature: the standardization procedures have not necessarily been rigorous enough. So sometimes you might find that actually if you use the proper procedures you will end up with a lower plasma zinc than you would otherwise have.

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