Zinc

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Importance of zinc for health

Zinc is a transition metal and an essential nutrient for humans. Zinc forms the catalytic centre of over 100 different enzymes responsible for many key physiological functions. Zinc is one of the most abundant elements within cells and has an essential role in cell growth, differentiation and metabolism on a cellular level (1, 2), and growth, development and immunity of the whole body (3). The most common cause of zinc deficiency worldwide is inadequate dietary intake of bioavailable forms of zinc. Zinc deficiency increases the risk of preterm birth, child diarrhoea and respiratory infections, and stunted linear growth (4). An estimated 116,000 child deaths are attributable to zinc deficiency each year.

Biological role of zinc

Zinc has catalytic, regulatory and structural roles in the cell (5) that influence reproduction, growth and immunity (6). More than 300 metalloenzymes require zinc as a catalyst, and -2500 transcription factors, or 8% of the human genome, require zinc for their structural integrity (7). Zinc is a type 2 nutrient that is part of general cellular metabolism (3). There is no specific tissue that acts as a zinc storage site during periods of dietary excess or from which it can be released when intakes are inadequate (3). Zinc homeostasis is thus achieved through a careful balance of absorption and excretion, and import and export at the cellular level (3). Zinc excretion appears to react more quickly to changes in intake while zinc absorption responds more slowly, but this synergistic mechanism can handle large fluctuations in zinc intake (5, 8). The body zinc pool must be sustained by a continual dietary supply that may be rapidly depleted when dietary zinc intakes are insufficient and prolonged (3).

Effects of zinc deficiency

Severe clinical zinc deficiency is rare and occurs most frequently in individuals with the genetic disorder acrodermatitis enteropathica, where infants are born with impaired gastrointestinal zinc transport; in those receiving total parenteral nutrition without zinc, following alcohol abuse and with penicillamine therapy (6). Untreated severe zinc deficiency may be fatal. Symptoms of severe zinc deficiency include dermatitis, alopecia, diarrhoea, weight loss, intercurrent infections due to immune dysfunction and neurosensory disorders (6).

Mild-to-moderate zinc deficiency is more common, but may be challenging to identify as the clinical picture resembles that of a generalised poor micronutrient status. An inadequate dietary intake is likely the principal cause of zinc deficiency worldwide, and is especially common in lower-income countries. This can be due to several factors, including consumption of foods that have limited bioavailable zinc, a low total dietary zinc intake, and a high consumption of foods high in phytate that can inhibit zinc absorption (5, 6, 9). **Mild-to-moderate zinc deficiency may have important health effects at a population level, including an increased susceptibility to diarrhoea and respiratory infections and an increased risk of stunting**. The amount of absorbable zinc in the national food supply, and the prevalence of stunting among children under five can serve as proxy indicators of the risk of deficiency in a population. Stunted children are at a higher risk of morbidity from infection and mortality as children and non-communicable diseases in later life, and less completed schooling and a higher risk of living in poverty as adults (4). Prevention of stunting and its associated causes corresponds to the United Nations Sustainable Development Goal #2.

WHO guidelines for zinc supplementation in children and pregnant women

Zinc supplementation in the management of diarrhoea. Therapeutic zinc supplementation reduces the duration and severity of diarrhoea in children. As part of the effective management of acute diarrhoea in children, the WHO recommends that mothers, other caregivers and health workers provide children with 20 mg of zinc per day (10 mg per day for infants under the age of six months) for 10-14 days along with oral rehydration solution. https://www.who.int/elena/titles/zinc_diarrhoea/en/

Zinc supplementation in children with respiratory infection. Several studies have reported that zinc supplementation may reduce the frequency and severity of respiratory infections in children, however results have been inconsistent. https://www.who.int/elena/titles/zinc_pneumonia_children/en/

Zinc supplementation and growth in children. The available evidence is inconsistent but suggests that zinc supplementation may help to improve linear growth of children under 5 years of age. https://www.who.int/elena/titles/zinc_stunting/en/

Zinc supplementation during pregnancy. Due to the key role of zinc in cell replication, protein synthesis and growth, zinc is an essential nutrient during pregnancy. During this time, zinc requirements increase due to demands of both the mother and foetus, and an increased turnover. Zinc supplementation during pregnancy given to mothers in low-income countries may help to reduce pre-term births (10) but there is no evidence to promote its use to prevent pre-eclampsia or low-birth weight, and no specific recommendations at this time. https://www.who.int/elena/titles/zinc_pregnancy/en/

Risks from excessive zinc intakes

Excessive zinc intake is rare in the general population.

Excessive intakes can occur in persons receiving zinc therapy for acrodermatitis enteropathica, decubitus ulcer healing, celiac disease, glucagonoma, hepatic encephalopathy, acne, and for reducing symptoms of the common cold (11). Consumption of excessive zinc for prolonged periods may interact with the absorption and/or metabolism of other trace elements in the body, particularly copper (11, 12). Copper may have a role in both humoral and cellular factors of the immune system (13), and a deficiency in copper may cause neurological effects including myelopathy, anaemia and neutropenia (11, 14, 15).

Human biomarkers of population zinc intake and status

There are currently three recommended strategies by the Biomarkers of Nutrition for Development (BOND) review group (7):

1. Plasma zinc status
2. Prevalence of stunting
3. Assessment of dietary zinc intake

Precise information from biochemical assessment of zinc status is currently limited. The World Health Organization (WHO) Vitamin and Mineral Nutrition Information Service (VMNIS) Micronutrients Database (https://www.who.int/vmnis/database/en/) report that only 17 countries have assessed zinc status using serum or plasma zinc as part of their national survey. Most estimations of risk of zinc deficiency are linked to dietary intake or to prevalence of stunting (16).

OpeN-Global, at present, covers only laboratory methods of biomarker assessment.

Currently, plasma (or serum) zinc is the recommended biomarker by IZiNCG, WHO, UNICEF, and IAEA (17), and by a systematic review and meta-analysis of data from 46 publications (18). Plasma/serum zinc assay methods are given below.

We provide OpeN-Global visitors seeking advice on assessment of stunting prevalence and/or dietary zinc intake, with signposting to relevant references and resources below.

Plasma or serum zinc

Plasma/serum zinc concentration reflects dietary zinc intake during the previous weeks, responds consistently to zinc supplementation, and reference data are available for most age and sex groups, making it an appropriate biomarker for use in research studies (e.g. to assess the response of a zinc supplementation intervention) and population health surveys alike.

Methods

Serum zinc concentration can be measured by atomic absorbance spectrometry (AAS), inductively couple plasma optical emission spectrometry (ICP-OES), and inductively coupled plasma mass spectrometry (ICP-MS) (7).

ICP-MS: For a method description, see: Thomas D. B. Lyon, Gordon S. Fell, Robert C. Hutton and Andrew N. Eaton. Evaluation of inductively coupled argon plasma mass spectrometry (ICP-MS) for simultaneous multi-element trace analysis in clinical chemistry. Journal of Analytical Atomic Spectrometry, 1988, 3 265-271.: https://pubs.rsc.org/en/content/articlelanding/1988/JA/JA9880300265#!divAbstract

For further methodological advice and guidance: see the Biomarkers of Nutrition for Development (BOND)—Zinc Review (7) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4807640/ and the IZiNCG Technical Brief no. 2: Assessing population zinc status with serum zinc concentration and no. 9: The value of measuring plasma or serum zinc concentrations in national surveys. https://www.izincg.org/technical-briefs

Confounding factors

Confounding factors such as infection can lower serum zinc concentrations, leaving to overestimation of zinc deficiency (19). Furthermore, plasma zinc concentrations can be influenced by other food intake, time of day, sex, age, pregnancy, oral contraceptive use, severe stress, position of subject during blood drawing, and length of time subject's arm is occluded with a tourniquet (7). Cut-offs may vary accordingly. See the IZiNCG's Technical Brief no. 2 (https://www.izincg.org/technical-briefs) and page on practical tips for zinc analysis (https://www.izincg.org/izincg-practical-tips), for advice on good blood collection techniques for zinc analysis.

Methodological considerations

Contamination: Zinc is present in serum and plasma only in very low concentrations. Thus, any contamination from external sources must be avoided as it can dramatically change the results. See IZiNCG's Technical Brief no. 2 (https://www.izincg.org/technical-briefs) the IZiNCG and page on practical tips for zinc analysis (https://www.izincg.org/izincg-practical-tips)

Haemolysis of blood sample: See IZiNCG Technical Brief no. 6: How to deal with haemolysis for plasma/serum zinc analysis: https://www.izincg.org/technical-briefs

See the section on Useful links below, for details on how to keep in touch with IZiNCG and get regular updates on new publications.

Interpretation

IZiNCG recommends that when the prevalence of a low plasma/serum zinc concentration is > 20%, the risk of zinc deficiency is considered elevated and should be addressed through public health interventions to improve zinc status (20, 21).

Further advice on statistical analysis and suggested lower cut-offs can be found on the IZiNCG page on practical tips for zinc analysis, https://www.izincg.org/izincg-practical-tips

See the section on Useful links below, for details on how to keep in touch with IZiNCG and get regular updates about new publications.

Other recommended markers of population zinc status

1. **Prevalence of stunting:**

Height- or length-for-age is the best-known functional outcome associated with the risk of zinc deficiency in populations. For population assessment, the advised indicator to use is the percentage of children under 5 years of age with length- or height-for age less than –2.0 SD below the age-specific median of the reference population.

The risk of zinc deficiency is considered elevated and of public health concern when the prevalence of low height- or length-for-age is greater than 20%.

For methods and advice, see:

IZiNCG resources available under *Assessment of Stunting* https://www.izincg.org/assessment-of-zinc-status

WHO pages: Stunting in a nutshell https://www.who.int/nutrition/healthygrowthproj_stunted_videos/en/

2. **Assessment of dietary zinc intake:**

Reliable methods have been developed to evaluate dietary zinc intakes and to assess the risk of inadequacy for individuals and population groups. As a result, vulnerable individuals can be identified for dietary counselling and at-risk subgroups in the population targeted for intervention programs.

For methods and advice, see IZiNCG technical brief no. 3 (https://www.izincg.org/technical-briefs) and further IZiNCG resources available under *Assessment of Dietary Zinc Intakes* https://www.izincg.org/assessment-of-zinc-status

For further information, see the Institute of Medicine Food and Nutrition Board guidance on Dietary Reference Intakes: applications in dietary assessment, available at https://www.ncbi.nlm.nih.gov/pubmed/25057725

Other methods

Hair or nail zinc

Analysis of scalp hair and nail zinc is a potential biomarker of zinc status which may have advantages for use in LMIC settings due to the ease of sampling, stability of samples, and lack of need for a cold chain. Hair zinc is classified as a potential- and nail zinc as an emerging- biomarker of zinc exposure by the BOND Zinc Expert Panel (7). Currently, they are not recommended as a single assessment indicator of zinc status. However, they are recommended for further development as more data are urgently needed to confirm their sensitivity and specificity to changes in zinc nutrition and to establish reference limits or true cutoffs indicative of zinc deficiency.

Method

For a method description, see the IZiNCG Technical Brief 8: Assessing population zinc exposure with hair or nail zinc. https://www.izincg.org/technical-briefs

Other methods include assessment of zinc-dependent proteins; oxidative stress and DNA integrity; zinc kinetics; taste acuity tests. OpeN-Global readers should consult the Biomarkers of Nutrition for Development (BOND)—Zinc Review https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4807640/ or the IZiNCG Technical Briefs (https://www.izincg.org/technical-briefs) and the IZiNCG pages on Assessment of Zinc Status (https://www.izincg.org/assessment-of-zinc-status/)

Quality Control

As described above, when measuring plasma or serum zinc concentration, it is important to remember that zinc is present in only very low concentrations and contamination from external sources (i.e. inappropriate supplies and materials, the environment) is easy. It is therefore important to maintain strict quality control procedures when collecting, storing and processing samples for analysis. See the description and links above for more details.

Laboratory accreditation and technical assistance

For all questions on laboratory accreditation and validation schemes for zinc assessment, as well as technical queries, please see the OpeN-Global page on laboratory quality assessment and accreditation (https://open-global.kcl.ac.uk/accreditation/), or write to OpeN-Global (https://open-global.kcl.ac.uk/contact/) or to IZiNCG (https://www.izincg.org/contact).

Useful links

IZiNCG: The International Zinc Nutrition Consultative Group (IZiNCG) is an international group whose primary objectives are to promote and assist efforts to reduce global zinc deficiency, with particular emphasis on the most vulnerable populations of low-income countries. IZiNCG provides technical assistance to researchers, public health professionals, national governments, and other agencies in LMICs who are interested in assessing zinc status and implementing zinc interventions. This includes freely-available online technical documents and briefs, and an email response team for questions related to zinc in public health. IZiNCG also works to connect individual researchers or public health workers with local or regional institutions with expertise in the field of zinc. The IZiNCG website provides a comprehensive resource for population zinc assessment, including background information on zinc, design and implementation of zinc assessment studies and interpreting population date. Access the IZiNCG website here.

IZiNCG contact for technical advice and queries: The IZiNCG secretariat are available to answer any questions about any aspect of population zinc assessment, including laboratory analyses. Find out how IZiNCG can help you, or use this link to go directly to their Contact form

All briefs are also available in French, Spanish and Portuguese via this page.

Biomarkers of Nutrition for Development: The Biomarkers of Nutrition for Development (BOND) project is designed to provide evidence-based advice to anyone with an interest in the role of nutrition in health. For a comprehensive review of zinc biology and biomarkers, including a background of zinc within public health, an overview of available biomarkers and considerations for their use including interpretation of zinc biomarkers across a range of clinical and population-based applications, OpeN-Global users are directed to the BOND review for zinc, available as an open-access resource here.

UNICEF data: UNICEF data can be used to access historical data complementary to population zinc intakes such as stunting prevalence and diarrhoeal disease. https://data.unicef.org

WHO Vitamin and Mineral Nutrition Information Service (VMNIS) includes the Micronutrients Database (http://www.who.int/vmnis/database/en/), which includes 40 indicators of the status of 17 micronutrients or micronutrient-related conditions, covering both deficiency and excess. The Micronutrients Database is an interactive platform for summarizing data published in reports and manuscripts on the micronutrient status of populations representative at the national, regional and first administrative level. It is also worth mentioning that nationally-representative data on plasma/serum zinc status is now available as part of the WHO Micronutrient Database/VMNIS. Maps can be generated, which show plasma zinc data at a national-level. The IZiNCG website has recently been updated to include this.

WHO e-Library of Evidence for Nutrition Actions (eLENA) has several useful resources on zinc:

- *Zinc supplementation in the management of diarrhoea*.
- *Zinc supplementation in children with respiratory infections*.
- *Zinc supplementation and growth in children*.

- *Zinc supplementation during pregnancy*.

Further reading

The 2013 Lancet series on Maternal and Child Nutrition gives estimates of the proportion of child deaths due to zinc deficiency and some useful general information on zinc.https://www.thelancet.com/series/maternal-and-child-nutrition

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