Zinc and Infant nutrition

Leigh Ackland[1*] and Agnes Michalczyk[1]

[1]Centre for Cellular and Molecular Biology, School of Life and Environmental Sciences, Deakin University, Burwood, Victoria, Australia 3125

Keywords: Zinc, infant nutrition, Zn deficiency, Zn bioavailability, Zn supplementation

***Corresponding author**:

M Leigh Ackland

Centre for Cellular and Molecular Biology, School of Life and Environmental Sciences,

Deakin University, Burwood, Victoria, Australia 3125

Phone: +61 3 92517036

Email: leigha@deakin.edu.au

Abstract:

Zinc is essential for a wide variety of cellular processes in all cells. It is a critical dietary nutrient, particularly in the early stages of life. In the early neonatal period, adequate sources of zinc can be obtained from breast milk. In rare circumstances, the mammary gland produces zinc deficient milk that is potentially lethal for exclusively breast-fed infants. This can be overcome by zinc supplementation to the infant. Alterations to key zinc transporters provide insights into the mechanisms of cellular zinc homeostasis. The bioavailability of zinc in food depends on the presence of constituents that may complex zinc. In many countries, zinc deficiency is a major health issue due to poor nourishment. Young children are particularly affected. Zinc deficiency can impair immune function and contributes to the global burden of infectious diseases including diarrhoea, pneumonia and malaria. Furthermore, zinc deficiency may extend its effects across generations by inducing epigenetic effects that alter the expression of genes. This review discusses the significance of adequate zinc nutrition in infants, factors that influence zinc nutrition, the consequences of zinc deficiency, including its contribution to the global burden of disease and addresses some of the knowledge gaps in zinc biology.

Introduction

Infancy is a critical phase of life that requires adequate nutrition to sustain growth and development. Pioneers in the field of zinc biology identified many years ago that at birth, a neonate has only small pools of metabolically available zinc, as evidenced by early onset growth failure in conditions of zinc restriction, despite the presence of normal tissue zinc levels [1]. Thus establishing the zinc requirements for infants has been of great importance. This chapter discusses the importance of zinc nutrition, sources of dietary zinc and its bioavailability, requirements for mineral supplementation, risk factors for zinc deficiency, the effects of zinc deficiency and its contribution to the global burden of disease. The consequences of mutations and epigenetic changes to key zinc transporters provide insights into the cellular mechanisms regulating zinc homeostasis that are of particular importance to the health and development of infants and young children.

Essentiality of zinc

Zinc has many diverse roles in biological processes. At the cellular and molecular level, zinc is required for the structural and catalytic function of hundreds of enzymes that regulate the major metabolic pathways of the body [2]. As a structural component of transcription factors [3], zinc has a key role in regulation of gene expression and is involved in signal transduction and neuronal transmission [4, 5]. Numerous cellular processes require zinc including cell proliferation, differentiation, apoptosis and the integrity of cellular membranes [6-9]. Zinc is essential for normal growth and development, for the immune response, and for cognitive function [10-12].

Nutrition and body zinc status

The concept of body zinc status is based on the notion of acquisition of zinc that is sufficient for optimal biological processes. Body zinc status may be a consequence of dietary zinc intake, phytate consumption, gastrointestinal health, rate of zinc excretion and reabsorption, and other factors, many of which are not clear [13]. As there are numerous biological functions of zinc, many measures of zinc status have been considered, including zinc levels blood, urine, hair, feces, sweat, and saliva [14]. No single body zinc compartment represents an adequate estimate of overall body zinc status [1, 15, 16]. The WHO/UNICEF/IAEA/IZCG bodies recommend the use of three indicators to assess zinc status at the population level: prevalence of intakes below the estimated average requirement, percentage of low serum zinc concentrations and percentage of children less than 5 years who are stunted (WHO/UNICEF/IAEA/IZCG [17] and reviewed in [14]. The development of better indicators for zinc status is a major future challenge in the field of zinc biology.

In term infants the reference range for serum zinc in (10 to 17 µmol/L) is similar to that of healthy adults. Zinc levels are generally highest at birth and gradually decrease to 4 months postpartum and then subsequently stabilizing at median levels [18-21]. The reference range for preterm infants at birth (74-146mcg/dL: 11-22 µmol/L) [22] is higher than that of normal term infants at birth, but progressively declines over the subsequent 6-12 weeks, correlating with rapid infant growth [23].

Dietary zinc requirements of infants

Dietary requirements for essential nutrients including zinc provide estimates of whether intakes are adequate for optimal body function. The RDA (recommended dietary allowance) is the daily intake amount of a nutrient that is considered to be sufficient to meet the requirements of 97.5% of healthy individuals over the age of 6 months. RDAs for zinc vary between different countries and range from 1.5 to 2 mg/day for 0-6 months of age, 3-8 mg/day for 7-12 months of age and 4-9 mg/day for 1-3 year olds [24]. Due to the demand for zinc in the growing infant, in relation to body size, the RDA for infants is greater than adults (for Australia the zinc RDA is 14mg/day for men and 8mg/day for women [25]. The RDA for premature babies is 0.4 to 0.5 mg/kg/day [22]. More accurate estimates of RDA will be made possible with improved indicators of zinc status.

Zinc in human breast milk and infant formulas

Neonates are born with a substantial storage of zinc (25% of total body zinc) bound primarily to metallothioneins in the liver that accumulate in the last trimester of gestation [26-28]. These hepatic zinc reserves are progressively reduced until they reach the constant level at approximately 4 months of age [28, 29]. However, unlike iron and copper, the major source of zinc in the neonatal period is breast milk [29]. The zinc concentration in human milk is highest in colostrum (approximately 8 mg/L) and then rapidly declines during the first week of lactation reaching 50% of initial concentration by day 7 of lactation. After the first week the decline in milk zinc concentration continues but is slower, reaching approximately 2 mg/L by 2 months, 1 mg/L by 6 months and dropping to about 0.5 mg/L by 12 months (summarised in [29-31]. For breast fed neonates, zinc concentrations in milk are considered to be adequate for the first 6 months of life but beyond that, despite an increase in the volume of milk consumed, zinc in breast milk is likely to be marginally adequate in the absence of a weaning diet (reviewed in [13, 30, 32].

For premature infants, the level of zinc in breast milk cannot compensate for the increased zinc demand of the premature neonate due to higher than normal zinc requirements, the small size of

liver with reduced zinc storage and a short gastrointestinal system [22, 29, 30, 33-35]. These factors put premature infants in negative zinc balance until approximately 2 months of age and necessitates the use of zinc supplementation from birth [29, 36].

The WHO recommends exclusive breastfeeding of infants until 6 months of age (WHO Infant and young children nutrition resolution [37]). Despite the range of benefits that breast feeding offers for growing infants, only 16% of the infants in USA are exclusively breastfed at 6 months of age [38]. The remainder of infants are either exclusively formula-fed or receive a combination of formulas and breast milk [13]. The zinc content of formula milk ranges from 0.11 – 0.57 mg/100ml [39]. The most common infant formulas used around the world are either cow's milk-based formulas or soy-based formulas. Zinc bioavailability from any of the formulas is lower than from human breast milk, even though formulas often contain the higher concentration of zinc than breast milk. Therefore, to reach recommended dietary allowance for infants, formula zinc supplementation is commonly practiced [39-49]

Zinc bioavailability in infant's diet

Stable isotope studies and zinc loading tests show that human milk has a greater zinc bioavailability than cow's milk and infant formulas [40, 41]. Zinc absorption in healthy adults was on average 41% from human milk, 28% from cow's milk, 31% from casein-based formula and only 14% from soy based formula [40]. A higher fractional absorption of zinc from human milk (54%) was found in infants [50]. An important factor in zinc bioavailability is the whey-to-casein ratio as zinc is more bioavailable from whey compared to casein [51-53]. In early lactation, human milk contains approximately 20% casein, and the whey-to-casein ratio is 80:20. This is the opposite to the cow's whey-to-casein ratio of 20:80. At the later stages of human lactation the whey-to-casein ratio changes to approximately 60:40 [54]. Zinc that is bound to casein is less bioavailable compared with zinc bound to whey proteins because micelles of highly phosphorylated casein in cow's milk strongly bind zinc, making it less bioavailable to infants [31]. In early infancy, a large proportion of casein consumed from cow's milk remains undigested and thus still binds zinc, possibly due to the low stomach acid secretion that results in incomplete digestion of the protein [31, 55, 56]. Human milk contains a lower concentration of casein than cow's milk and has less zinc-binding phosphate groups on casein, thus only 15% of total milk zinc is bound to casein [57]. In human adults, zinc absorption from a casein-predominant milk formula was significantly lower than from a whey-predominant formula [51].

Approximately 85% of zinc in human milk is bound to whey proteins, low-molecular-weight ligands and fat globules [57]. The main components of whey proteins in human milk that bind zinc are serum albumin, α-lactalbumin and possibly lactoferrin. [58, 59]. The major milk protein α-lactalbumin which comprises 20-25% of total milk proteins binds zinc, and may facilitate its absorption [59]. Lactoferrin may also be a major zinc-binding protein from which zinc is absorbed [53], although another study reported that lactoferrin could only bind zinc *in vitro* at high zinc concentrations [57, 60].

Human milk contains a number of low-molecular-weight factors including peptides, amino acids and growth factors. Of these, a major zinc binding ligand was identified to be citrate. Citrate is an efficient zinc chelator and binds approximately 23% of the zinc associated with low molecular mass ligands in milk [61]. The addition of citrate to milk formulas had a positive effect on zinc absorption in suckling rats [62].

Dietary factors influencing zinc nutrition in infants

Micronutrient interactions can affect zinc bioavailability and absorption. This can be through competition of transport processes or through zinc chelation. Iron supplements may interfere with zinc absorption [63, 64]. Cadmium can inhibit zinc absorption while some amino acids including histidine and methionine increase zinc absortion [65]. Dietary zinc bioavailability is influenced by many food constituents including phytate, a plant ligand of inositol phosphate that is present in cereals and legumes [66]. Phytate is a form in which phosphorus is stored in cereals, legumes and other plants. Phytates form poorly soluble complexes with zinc that reduce zinc absorption [67].

Vegetarianism

Meat and seafood are major sources of dietary zinc, while the zinc in plant-based diets containing folate, fibre and phytochemicals, is less available [68]. Although grains, nuts and seeds can provide amounts of zinc similar to those found in animal tissues, adult populations with vegetarian diets have been found to have low zinc intakes [69-72] and in some cases reduced serum zinc levels [73]. Other studies on adults show no effects of vegetarian diets on serum zinc [70, 72, 74]. In young vegetarians, no differences in serum zinc between vegetarians and omnivores have been found [75].

Less information is available on zinc intakes and serum levels of infants and children who are vegetarians. National surveys in the United States estimate that 0.7 % of children aged 6 to 12 years are vegetarians and 1% of children in New Zealand between 5 to 14 years are vegetarians

while 2% of children in the UK and Australia are vegetarian (see Foster and Samman 2014 for a review [67]. In the Australian study, there were no differences in plasma zinc levels in children 1.5-4.5 years between vegetarians and omnivores, suggesting that adequate zinc is being provided by vegetarian diet [67]. In a review of zinc status of vegetarian and non-vegetarian children, no differences in serum zinc levels were seen in the three studies that were carried out [67]. However, on the basis of the lower zinc bioavailability in plants compared to animals, and the higher demand for zinc during growth, zinc supplementation has been recommended for vegetarian infants compared with non-vegetarians infants [67, 73, 75].

Effect of maternal zinc status on infant health

Although 82% of all pregnant women worldwide are estimated to be zinc deficient [76], zinc levels in human milk were found to be unrelated to maternal zinc status as measured by maternal plasma zinc levels [77], and the zinc status of the lactating mother does not influence transfer of zinc into milk [78-85]. Additionally, the majority of studies show no correlation between maternal age, parity or smoking habits on zinc levels in milk [78, 86-94].

Maternal factors, however, may play an important role in influencing the health of the subsequent generation, from infancy onwards. Mice studies carried out by Hurley and Keen in the 1980s have shown a contribution of maternal zinc deficiency to changes, later identified as epigenetic changes, adversely affect the next generation [95, 96]. Persistent effects of zinc deficiency have been observed across generations. Offspring of mice fed a zinc-deficient diet (60-70% of the control dietary zinc) from day 7 of gestation showed reduced levels of IgM. The reduced IgM levels persisted into the subsequent second and third generations of animals despite a zinc-replete diet. There were no overt signs of zinc deficiency in the zinc-deprived dams [97]. Cross-fostering of the offspring from zinc-deprived animals did not ameliorate some of the immunoglobulin abnormalities. Significantly, this demonstrates the importance of maternal nutrition to the health of subsequent generations. In humans, zinc deficiency during pregnancy has effects on the immune system of the fetus and reduces the size of the thymus and spleen and impairs the function of lymphocytes and neutrophils of the infant [98]. Maternal factors including age and BMI can affect subsequent generations through epigenetic mechanisms of which DNA methylation is a key process [99]. DNA methylation of zinc transporter gene ZnT5 was inversely correlated with length of gestation [99] providing evidence of maternal epigenetic effects on the subsequent generation. Zinc treatment increased histone H3 and H4 protein levels in cultured human neuronal cells providing a mechanism for the alteration of global gene expression levels [100]. A challenge in this area is to

understand how zinc deficiency during pregnancy influences the immune function of subsequent generations, including the early stages of life.

Zinc deficiency in infants

Zinc deficiency is a prevalent condition in countries with poor nourishment and particularly affects infants and young children. Due to the numerous roles of zinc in cell growth, differentiation and function and the lack of body stores, the infant is particularly susceptible to the adverse effects of zinc deficiency. Zinc deficiency accounts for the deaths of over half a million infants and children under 5 years of age, per year [13]. The WHO estimates that 800,000 deaths per year are due to zinc deficiency and that 50% of these are infants under the age of 5 years. [13]. Zinc deficiency contributes to the global burden of infectious disease through reducing immune function. Zinc deficiency in children aged less than 5 years old increases the incidence of diarrhoeal disease by 1.28, pneumonia by 1.52 and malaria by 1.56 [101, 102]. Based on these data zinc deficiency has been estimated to cause 176,000 diarrheal deaths, 406,000 pneumonia deaths and 207,000 malaria deaths. A recent analysis estimated the total mortality due to zinc deficiency to be 97,330 with a DALY of 9.14 million, ranking zinc deficiency 31st of the common risk factors contributing to the global burden of disease [103].

Cells with a rapid rate of turnover such as those of the immune, gastrointestinal systems, and skin are particularly vulnerable to zinc deficiency, accounting for the initial effects of dermatitis, diarrhoea, alopecia and loss of appetite [104, 105]. Severe zinc depletion for one month leads to hair, skin and mucous membrane changes, weight loss and growth retardation [13] that can become fatal in newborns [32]. Zinc deficiency impairs both the specific and the non-specific immune system that results in increased susceptibility to bacterial, viral and fungal pathogens [106].

At a population level, zinc deficiency is recognized as a public health problem. In 1961 in Iran children with dwarfism, hypogonadism, hepatosplenomegaly, dry skin and mental lethargy were described [107]. These features were later found to be caused by zinc deficiency and resolved following zinc supplementation [108]. Higher rates of infectious diseases including skin infections, diarrhea, respiratory infections and malaria were also noted [109].

Persistent mild to moderate zinc deficiency leads to growth stunting, poor appetite, impaired taste and smell, irritability and decrease resistance to infections [10, 102]. This type of zinc deficiency develops in infants usually due to the decline of zinc content in human milk [90, 110]. Infants who

are at risk of zinc deficiency include older exclusively breastfed infants, infants with low zinc intakes, premature and low birth weight infants, and those with diseases that impair gastrointestinal absorption [111, 112]. A number of diseases may predispose individuals to zinc deficiency, including untreated coeliac disease, Crohn's disease, bowel conditions, and diarrhoea [13]. Symptoms of zinc deficiency are non-specific and this may lead to a lack of recognition of this problem. Mild zinc deficiency may pass undetected due to the lack of specific biomarkers [111] and in industrialised countries, identification of marginal zinc deficiency may be pertinent due to its insidious nature and the consumption of processed foods. In future, increased knowledge of the molecules involved in maintenance of zinc homeostasis may lead to the development of tests for marginal zinc deficiency that is a consequence of poor nutrition or other factors. This could be particularly important for detecting zinc deficiency in infants prior to the development of the clinical features of zinc deficiency.

Zinc supplementation

Preterm babies represent approximately about 12% of births in USA, and have a higher risk of micronutrient deficiency than term babies [113]. Zinc fortification of this group has been recommended [114]. Preterm babies are recommended to have zinc supplements ranging from 200-500 µg/kg/day for infants born between 27 to 40 weeks gestation [22]. Very low birthweight premature infants, less than 1.5 kg at birth are recommended to have supplementation of 10 mg Zn/day beginning at week 1 until 42 weeks postpartum [115]. Maternal zinc supplementation of breastfeeding mothers is not considered as an effective treatment as it does not affect milk zinc levels [116].

Interventions to reduce zinc deficiency can have a huge impact on reducing the global burden of disease. Zinc supplementation reduces childhood mortality in countries where malnutrition and micronutrient deficiencies are prevalent [117]. As diarrhea and pneumonia are the two most common causes of childhood deaths in developing countries, zinc supplements are one of the proposed methods for reducing childhood mortality [118]. Analysis of zinc supplementation trials shows success in reduction of diarrhea and pneumonia at the population level [10, 102, 119]. Zinc supplementation reduced the prevalence of diarrhea by 25% and the incidence of pneumonia by 41% [120]. Evidence suggests that zinc supplementation also reduces childhood mortility [102, 121]. A systematic review of 20 independent intervention trials where zinc supplementation (5-50 mg/day was provided to pregnant women showed a small decrease in risk of pre-term birth [122].

Genetic conditions in infants that are associated with zinc deficiency

The most frequently occurring form of zinc deficiency is due to nutritional insufficiency. Rarer forms of zinc deficiency that are inherited may be found in exclusively breast-fed babies, who present with symptoms characteristic of nutritional zinc deficiency, including dermatitis, diarrhoea, alopecia, loss of appetite, impaired immune function and neuropsychiatric changes [109, 123]. This type of zinc deficiency (transient neonatal zinc deficiency) is caused by reduced levels of zinc in the milk and is found more commonly in pre-term babies (27 to 33 weeks gestation), compared to term babies [123-130]. Zinc levels in the milk of such zinc-deficient breast fed babies can be less than 90% that of normal milk at matched weeks of lactation [127, 128, 131] and it was established that maternal zinc deficiency was not the cause for the low zinc levels in breast). This form of neonatal zinc deficiency is most likely due to the higher zinc requirements of premature babies who also have a reduced capacity to absorb zinc from their gut [132]. In term infants however, the etiology of the transient zinc deficiency is not well understood, although a genetic component has recently been revealed.

Twenty four zinc transporter genes belonging to two main families, *SLC30A* and *SLC39A* have been identified [133]. The protein products of these genes are membrane-spanning molecules, many of which have been demonstrated to mediate zinc transport. Fourteen members of *SLC39* or *ZIP* family [134] and ten members of the *ZnT* family have been identified in mammalian cells [135]. Genetic studies have established that the neonatal zinc deficiency caused by reduced zinc levels in human milk is linked to mutations in *SLC30A2* (*ZnT2*). Different mutations have been found in *SLC30A2*. These include a missense mutation that substituted a conserved histidine, at amino acid 54, with arginine (H54R) [136] and a glycine to arginine substitution (G87R) [137] that reduced zinc concentrations in milk by more than 75%. Reductions in milk zinc levels to below 90% of normal were found associated with missense mutations where a tryptophan residue substituted for an arginine residue (W152R), and where a serine residue substituted for a leucine residue (S296L) [131]. Other studies have reported non-synonymous variations and polymorphisms in *ZnT2/SLE30A2* that correlated with zinc levels in milk. In milk collected from a population of 54 exclusively breast feeding mothers, non-synonymous variations in SLC30A2 were found in 36% of women, which were associated with variations in milk zinc concentrations [138]. *In vitro* characterization indicated that some of these variants showed inappropriate cellular localization and altered subcellular zinc localization. In a another study of 750 breastfeeding women, variations in the milk zinc levels were associated with polymorphisms in *SLC30A2* found in 9.7% of women, including -697G>T in the NF-1/L regulatory region of the *SLC30A2* promotor, that may reduce its

transcription to cause low milk zinc levels. Additionally, two polymorphisms in the *SLC30A2* coding region lysine substituted for arginine (K344R) or for leucine substituted by proline (L23P) were associated with low levels of zinc in milk [139]. The L23P substitution was previously described to cause mislocalisation of the SLC30A2 protein to lysosomes instead of secretory endosomes, thus potentially affecting zinc secretion in mammary cells [140]. Thus genetic variations in *ZnT2* may have consequences for infant growth and development by influencing the transport of zinc into milk.

Other cases of neonatal zinc deficiency due to reduced levels of zinc in human milk are linked to reduced expression of two other zinc transporters, SLC30A5 and SLC30A6. In these cases SLC30A5 and SLC30A6 protein levels in white blood cells isolated from women with infants afflicted with neonatal zinc deficiency were reduced compared to cells isolated from non-affected women. Analysis of the promoter regions of the *SLC30A5* and *SLC30A6* genes revealed cell-specific epigenetic changes between affected and unaffected mothers. In maternal lymphoblasts, CpG site 2 in *SLC30A5* was significantly less methylated in affected mothers with compared with unaffected mothers while in maternal fibroblasts CpG site 2 in *SLC30A5* was significantly more methylated. Thus modified expression of *SLC30A5* may account for the reduced activity of SLC30A5 and low levels of zinc in milk [141].

Further studies are required to clarify the specific cellular roles of all the family members of the zinc transporters in zinc homeostasis in growth and development. Greater knowledge of the genetic and epigenetic variants of zinc transporters in different tissues and how these impact on zinc homeostasis is essential, particularly in organs such as the mammary gland and the gut that play key roles in the delivery of nutrients. Such information will provide insights into how such variants impact on growth and development during infancy. Knowledge of the precise cellular function of zinc transporters may lead to the development of novel markers to assess zinc status.

A murine disorder termed ‘lethal milk’ has a phenotype similar to the human condition including a 30% reduction in milk zinc levels, where newborn pups nursed on homozygous mutant lethal milk dams develop lethal zinc deficiency within a week and die [142]. A defect in the secretion of zinc from the murine mammary gland was demonstrated [143, 144], and later linked to a mutation in another zinc transporter SLC30A4 [145]. Mutations in *SLC30A4* were not found in several cases of neonatal zinc deficiency in humans [132], indicating that human and mouse conditions while having some phenotypic similarities, have different underlying causes.

Alternatively, zinc deficiency may result from impaired zinc absorption in the gut, as in acrodermatitis enteropathica (AE)[123]. Patients with AE were subsequently shown to have reduced intestinal absorption and intestinal secretion of zinc [146, 147]. This disorder usually develops after weaning as the zinc in human milk is more bioavailable than from other food sources [148]. AE is the most commonly described inherited form of zinc deficiency, first reported in 1902 [149] and later described in more detail [150]. The symptoms of AE are similar to nutritional zinc deficiency and include skin lesions, alopecia, diarrhoea, neuropsychological disturbances, reduced immune function and death of patients in the absence of treatment [105]. AE was first identified as a zinc deficiency disease following successful resolution of symptoms with oral zinc supplementation [151]. Zinc replacement therapy commencing at 3 mg/kg/d of elemental zinc is recommended [152].

Diagnosis of AE may be problematic. The disease is rare and the characteristic erythematous rash is not confined to AE and may occur in other dermatological conditions [153]. Symptoms of zinc deficiency due to nutritional problems occur in digestive, pancreatic or hepatic diseases, and AE-like disorders can be a consequence of deficiencies of other nutrients including amino acids and in metabolic disorders ([153].

Generally, the plasma levels of zinc in patients with AE who are untreated, are reduced (ranging from 0.33µmol/L to 8.1µmol/L) [154-159] however normal (11.5-22.5µmol/L) [154, 160] and higher (23.2µg/g dry weight relative to normal 10.4-11.9µg/g dry weight) [161] serum zinc levels have been reported. AE is successfully treated with 1-3mg/day of elemental zinc that results in the resolution of symptoms within days or weeks [141].

Defects in the *SLC39A4* gene were identified as being responsible for AE [162, 163]. Deletions or insertions, premature terminations, frameshifts, splice-site defects, and polymorphisms in the promoter region of the gene account for 41 mutations or variants of ZIP4 reported in patients with the disorder [164]. The *hZIP4* gene is expressed in the small intestine, stomach, colon and kidney [162], accounting for the reduced zinc absorption. In some patients with symptoms of AE, no defects in SLC39A4 have been found suggesting other causes of this disease, possibly defects in other zinc transporters [165]. The genetic defects in the zinc transporters that result in zinc deficiency indicate the importance of zinc transporters in normal zinc homeostasis.

In conclusion, zinc is critical for infant growth and development. Zinc deficiency is a major global health issue that particularly affects young children and contributes to the global burden of infectious diseases including diarrhoea, pneumonia and malaria. As zinc is essential for immune function, its deficiency is a key factor in the increased susceptibility to infection found in states of nutritional deficiency. Mutations in zinc transporter genes provide insights into the mechanisms of cellular zinc homeostasis. There is also evidence that zinc deficiency induces epigenetic effects that may affect subsequent generations. Future research is needed to clarify the functions of the SLC30A and SLC39A family members as well as other potential zinc transporters, in health and disease states, and to develop better markers for assessment of zinc status.

References:

[1] P.J. Aggett, The Proceedings of the Nutrition Society 50 (1991) 9-17.
[2] B.L. Vallee, D.S. Auld, Biochemistry 29 (1990) 5647-5659.
[3] J.M. Berg, Science 232 (1986) 485-487.
[4] K. Murakami, M.K. Whiteley, A. Routtenberg, The Journal of biological chemistry 262 (1987) 13902-13906.
[5] S.Y. Assaf, S.H. Chung, Nature 308 (1984) 734-736.
[6] K.H. Falchuk, Molecular and cellular biochemistry 188 (1998) 41-48.
[7] J.M. Ryu, M.Y. Lee, S.P. Yun, H.J. Han, Journal of cellular physiology 218 (2009) 558-567.
[8] P.D. Zalewski, I.J. Forbes, W.H. Betts, The Biochemical journal 296 (1993) 403-408.
[9] J.E. Coleman, Annual review of biochemistry 61 (1992) 897-946.
[10] R.E. Black, S. Sazawal, The British journal of nutrition 85 Suppl 2 (2001) S125-129.
[11] H. Haase, L. Rink, Metallomics : integrated biometal science 6 (2014) 1175-1180.
[12] W. Maret, H.H. Sandstead, Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements 20 (2006) 3-18.
[13] N.F. Krebs, L.V. Miller, K.M. Hambidge, Paediatrics and international child health 34 (2014) 279-288.
[14] R.S. Gibson, S.Y. Hess, C. Hotz, K.H. Brown, The British journal of nutrition 99 Suppl 3 (2008) S14-23.
[15] B.L. O'Dell, The Journal of nutrition 126 (1996) 2342S-2344S.
[16] C. Hotz, N.M. Lowe, M. Araya, K.H. Brown, The Journal of nutrition 133 (2003) 1563S-1568S.
[17] Food and nutrition bulletin 28 (2007) S399-S400.
[18] S. Jyotsna, A. Amit, A. Kumar, Journal of clinical and diagnostic research : JCDR 9 (2015) SC01-03.
[19] T.A. Ozden, G. Gokcay, M.S. Cantez, O. Durmaz, H. Issever, B. Omer, G. Saner, BMC pediatrics 15 (2015) 157.
[20] C.N. Lin, A. Wilson, B.B. Church, S. Ehman, W.L. Roberts, G.A. McMillin, Clinica chimica acta; international journal of clinical chemistry 413 (2012) 612-615.
[21] A. Higashi, T. Ikeda, I. Uehara, I. Matsuda, The Tohoku journal of experimental medicine 137 (1982) 41-47.
[22] C.W. Finch, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition 30 (2015) 44-58.
[23] P.J. Aggett, Acta paediatrica 402 (1994) 75-82.

[24] F.Z. Wang, l., in: J.O.S. Nriagu, E.P. (Ed.), Trace minerals and infectious diseases, Massachusetts Institute of Technology and the Frankfurt Institute for Advanced Studies, Cambridge, Massachusetts, USA, 2015, pp. 83-98.
[25] N.H.M.R. Council, Nutrient reference values for Australia and New Zealand: including recommended dietary intakes, in: N.H.a.M.R. Concil (Ed.), National Health and Medical Research Concil, Canberra, Australia, 2006.
[26] J.G. Dorea, M. Brito, M.O.G. Araujo, Journal of the American College of Nutrition 6 (1987) 491-495.
[27] P. Coni, A. Ravarino, A.M. Farci, F. Callea, P. Van Eyken, R. Sciot, R. Ambu, A. Marras, V. Costa, G. Faa, V.J. Desmet, J Pediatr Gastroenterol Nutr 23 (1996) 125-129.
[28] S.H. Zlotkin, M.G. Cherian, Pediatr Res 24 (1988) 326-329.
[29] N.F. Krebs, Journal of mammary gland biology and neoplasia 4 (1999) 259-268.
[30] J.G. Dorea, Nutr Res 20 (2000) 1645-1687.
[31] B. Lonnerdal, Physiological reviews 77 (1997) 643-669.
[32] A.S. Prasad, Journal of the American College of Nutrition 15 (1996) 113-120.
[33] E. Aquilio, R. Spagnoli, S. Seri, G. Bottone, G. Spennati, Biological trace element research 51 (1996) 63-70.
[34] J.K. Friel, W.L. Andrews, S.E. Jackson, H.P. Longerich, C. Mercer, A. McDonald, B. Dawson, B. Sutradhar, Biological trace element research 67 (1999) 225-247.
[35] I.J. Griffin, M. Domellof, J. Bhatia, D.M. Anderson, N. Kler, Early human development 89 Suppl 2 (2013) S29-34.
[36] K.M. Hambidge, N.F. Krebs, J.E. Westcott, L.V. Miller, The Journal of pediatrics 149 (2006) S64-68.
[37] W.H. Organisation, Infant and young children nutrition resolution World Health Organisation, Geneva, Switzerland, 2001.
[38] C.f.d.c.a. prevention, CDC 24/7 (2015).
[39] I. Lombeck, A. Fuchs, European journal of pediatrics 153 (1994) 770-776.
[40] B. Sandstrom, A. Cederblad, B. Lonnerdal, American journal of diseases of children 137 (1983) 726-729.
[41] C.E. Casey, P.A. Walravens, K.M. Hambidge, Pediatrics 68 (1981) 394-396.
[42] E. Riva, E. Verduci, C. Agostoni, M. Giovannini, The Journal of international medical research 35 (2007) 20-37.
[43] M.L. Moraes, M.B.S. Feijo, F.M. Melo, R.C. Campos, R.A. Hauser-Davis, J Brazil Chem Soc 20 (2009) 1724-1731.
[44] B. Lonnerdal, Journal of Nutrition 119 (1989) 1839-1845.
[45] L. Salmenpera, J. Perheentupa, P. Pakarinen, M.A. Siimes, American Journal of Clinical Nutrition 59 (1994) 985-989.
[46] Y.H. Han, M. Yon, H.S. Han, K.E. Johnston, T. Tamura, T. Hyun, Nutr Res Pract 5 (2011) 46-51.
[47] A. Molska, I. Gutowska, I. Baranowska-Bosiacka, I. Nocen, D. Chlubek, Biological trace element research 158 (2014) 422-427.
[48] S. Fernandez-Menendez, M.L. Fernandez-Sanchez, B. Fernandez-Colomer, R.R. de la Flor St Remy, G.D. Cotallo, A.S. Freire, B.F. Braz, R.E. Santelli, A. Sanz-Medel, Journal of chromatography. A 1428 (2016) 246-254.
[49] S.A. Atkinson, J Pediatr Gastroenterol Nutr 30 (2000) 8-9.
[50] N.F. Krebs, C.J. Reidinger, L.V. Miller, K.M. Hambidge, Pediatr Res 39 (1996) 661-665.
[51] B. Lonnerdal, A. Cederblad, L. Davidsson, B. Sandstrom, The American journal of clinical nutrition 40 (1984) 1064-1070.
[52] R.J. Cousins, K.T. Smith, The American journal of clinical nutrition 33 (1980) 1083-1087.
[53] P. Blakeborough, D.N. Salter, M.I. Gurr, The Biochemical journal 209 (1983) 505-512.
[54] C. Kunz, B. Lonnerdal, Acta Paediatr 81 (1992) 107-112.

[55] G. Harzer, H. Kauer, The American journal of clinical nutrition 35 (1982) 981-987.
[56] S. Mason, Arch Dis Child 37 (1962) 387-&.
[57] B. Lonnerdal, B. Hoffman, L.S. Hurley, The American journal of clinical nutrition 36 (1982) 1170-1176.
[58] B. Lonnerdal, in: T.W.L. Hutchens, B.; Rumball, S. (Ed.), Lactoferrin: Structure and Function, Plenum Press, New York, 1994, pp. 171-177.
[59] B. Lonnerdal, E.L. Lien, Nutrition reviews 61 (2003) 295-305.
[60] B. Lonnerdal, Progress in food & nutrition science 9 (1985) 35-62.
[61] R. Milacic, D. Ajlec, T. Zuliani, D. Zigon, J. Scancar, Talanta 101 (2012) 203-210.
[62] M.L. Pabon, B. Lonnerdal, Nutr Res 13 (1993) 103-111.
[63] B. Sandstrom, The British journal of nutrition 85 Suppl 2 (2001) S181-185.
[64] N.W. Solomons, The Journal of nutrition 116 (1986) 927-935.
[65] B. Lonnerdal, The Journal of nutrition 130 (2000) 1378S-1383S.
[66] H.H. Sandstead, J.H. Freeland-Graves, Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements 28 (2014) 414-417.
[67] M. Foster, S. Samman, Advances in food and nutrition research 74 (2015) 93-131.
[68] J.H. Freeland-Graves, M.L. Ebangit, P.W. Bodzy, Journal of the American Dietetic Association 77 (1980) 648-654.
[69] U.M. Donovan, R.S. Gibson, The Journal of adolescent health : official publication of the Society for Adolescent Medicine 18 (1996) 292-300.
[70] J.R. Hunt, L.A. Matthys, L.K. Johnson, The American journal of clinical nutrition 67 (1998) 421-430.
[71] K.C. Janelle, S.I. Barr, Journal of the American Dietetic Association 95 (1995) 180-186, 189, quiz 187-188.
[72] J.H. Freeland-Graves, P.W. Bodzy, M.A. Eppright, Journal of the American Dietetic Association 77 (1980) 655-661.
[73] M. Foster, A. Chu, P. Petocz, S. Samman, Journal of the science of food and agriculture 93 (2013) 2362-2371.
[74] M.J. Ball, M.L. Ackland, The British journal of nutrition 83 (2000) 27-33.
[75] R.S. Gibson, A.L. Heath, E.A. Szymlek-Gay, The American journal of clinical nutrition 100 Suppl 1 (2014) 459S-468S.
[76] L.E. Caulfield, N. Zavaleta, A.H. Shankar, M. Merialdi, The American journal of clinical nutrition 68 (1998) 499S-508S.
[77] M. Domellof, B. Lonnerdal, K.G. Dewey, R.J. Cohen, O. Hernell, The American journal of clinical nutrition 79 (2004) 111-115.
[78] R.M. Feeley, R.R. Eitenmiller, J.B. Jones, H. Barnhart, American Journal of Clinical Nutrition 37 (1983) 443-448.
[79] P.B. Moser, R.D. Reynolds, The American journal of clinical nutrition 38 (1983) 101-108.
[80] N.F. Krebs, K.M. Hambidge, M.A. Jacobs, J.O. Rasbach, The American journal of clinical nutrition 41 (1985) 560-570.
[81] M.V. Karra, A. Kirksey, J Pediatr Gastr Nutr 7 (1988) 100-106.
[82] P.B. Moser, R.D. Reynolds, S. Acharya, M.P. Howard, M.B. Andon, S.A. Lewis, The American journal of clinical nutrition 47 (1988) 729-734.
[83] S. Sazawal, R.E. Black, M.K. Bhan, S. Jalla, N. Bhandari, A. Sinha, S. Majumdar, The Journal of nutrition 126 (1996) 443-450.
[84] T.M. Samuel, T. Thomas, P. Thankachan, S. Bhat, S.M. Virtanen, A.V. Kurpad, Maternal & child nutrition 10 (2014) 398-409.
[85] R. Chierici, D. Saccomandi, V. Vigi, Acta paediatrica 88 (1999) 7-13.
[86] G.F. Kirsten, V.H.H. de, S. de Villiers, W.S. Dempster, F. Pocock, H. Varkevisser, South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 67 (1985) 414-418.

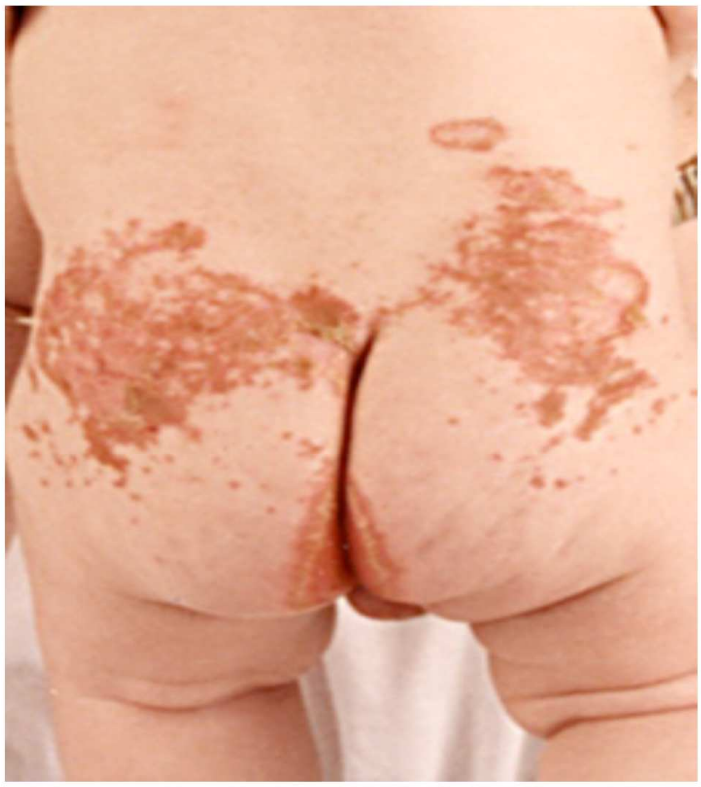
[87] J.A. Lamounier, J.C. Danelluzzi, H. Vannucchi, Journal of tropical pediatrics 35 (1989) 31-34.
[88] A. Jendryczko, M. Drozdz, K. Magner, J. Tomala, Acta physiologica Polonica 35 (1984) 219-223.
[89] M. Hussain, Z.U. Sikder, M.A. Wahed, A.T. Haque, F. Jahan, Bangladesh Medical Research Council bulletin 22 (1996) 70-73.
[90] C.J. Bates, H. Tsuchiya, European journal of clinical nutrition 44 (1990) 61-69.
[91] K.K. Lehti, European journal of clinical nutrition 44 (1990) 675-680.
[92] P. Melnikov, A.J. da Cruz Montes Moura, D. Batista Palhares, C.S. Martimbianco de Figueiredo, Indian pediatrics 44 (2007) 355-357.
[93] E. Orun, S.S. Yalcin, O. Aykut, G. Orhan, G.K. Morgil, Indian pediatrics 49 (2012) 133-135.
[94] S.S. Yalcin, S. Yalcin, A.I. Gucus, Pediatrics 135 (2015) S13-+.
[95] L.S. Hurley, Philosophical transactions of the Royal Society of London. Series B, Biological sciences 294 (1981) 145-152.
[96] C.L. Keen, L.S. Hurley, Neurotoxicology 8 (1987) 379-387.
[97] R.S. Beach, M.E. Gershwin, L.S. Hurley, Science 218 (1982) 469-471.
[98] N. Wellinghausen, The British journal of nutrition 85 Suppl 2 (2001) S81-86.
[99] J.A. McKay, A. Groom, C. Potter, L.J. Coneyworth, D. Ford, J.C. Mathers, C.L. Relton, PloS one 7 (2012) e33290.
[100] C. Suphioglu, N. Sadli, D. Coonan, L. Kumar, D. De Mel, J. Lesheim, A.J. Sinclair, L. Ackland, The British journal of nutrition 103 (2010) 344-351.
[101] L.E. Caulfield, S.A. Richard, R.E. Black, The American journal of tropical medicine and hygiene 71 (2004) 55-63.
[102] R.E. Black, The Journal of nutrition 133 (2003) 1485S-1489S.
[103] S.S. Lim, T. Vos, A.D. Flaxman, G. Danaei, K. Shibuya, H. Adair-Rohani, M. Amann, H.R. Anderson, et al Lancet 380 (2012) 2224-2260.
[104] P.J. Aggett, in: C.F. Mills (Ed.), Zinc in Human Biology, Springer-Verlag, London, 1989, pp. 259-279.
[105] P.J. Aggett, J Inherit Metab Dis 1 (1983) 39-43.
[106] K.H. Ibs, L. Rink, The Journal of nutrition 133 (2003) 1452S-1456S.
[107] A.S. Prasad, J.A. Halsted, M. Nadimi, The American journal of medicine 31 (1961) 532-546.
[108] A.S. Prasad, A.J. Miale, Z. Farid, H.H. Sandstead, A.R. Schulert, J. Lab Clin Med 61 (1963) 537-549.
[109] A.S. Prasad, Annual review of nutrition 5 (1985) 341-363.
[110] M. Ohtake, T. Tamura, Journal of nutritional science and vitaminology 39 (1993) 189-200.
[111] N.F. Krebs, Annals of nutrition & metabolism 62 Suppl 1 (2013) 19-29.
[112] G. Terrin, R. Berni Canani, M. Di Chiara, A. Pietravalle, V. Aleandri, F. Conte, M. De Curtis, Nutrients 7 (2015) 10427-10446.
[113] S.A. Abrams, The American journal of clinical nutrition 98 (2013) 1373-1374.
[114] M. Domellof, World review of nutrition and dietetics 110 (2014) 121-139.
[115] G. Terrin, R. Berni Canani, A. Passariello, F. Messina, M.G. Conti, S. Caoci, A. Smaldore, E. Bertino, M. De Curtis, The American journal of clinical nutrition 98 (2013) 1468-1474.
[116] C.S. de Figueiredo, D.B. Palhares, P. Melnikov, A.J. Moura, S.C. dos Santos, Biological trace element research 136 (2010) 1-7.
[117] S. Bhatnagar, Lancet 369 (2007) 885-886.
[118] J.K. Das, R.A. Salam, Z.A. Bhutta, Current opinion in infectious diseases 27 (2014) 451-458.
[119] J.K. Das, R. Kumar, R.A. Salam, Z.A. Bhutta, Annals of nutrition & metabolism 62 Suppl 1 (2013) 44-56.

[120] Z.A. Bhutta, R.E. Black, K.H. Brown, J.M. Gardner, S. Gore, A. Hidayat, F. Khatun, R. Martorell, N.X. Ninh, M.E. Penny, J.L. Rosado, S.K. Roy, M. Ruel, S. Sazawal, A. Shankar, The Journal of pediatrics 135 (1999) 689-697.
[121] M.E. Penny, Annals of nutrition & metabolism 62 Suppl 1 (2013) 31-42.
[122] B.W. Chaffee, J.C. King, Paediatric and perinatal epidemiology 26 Suppl 1 (2012) 118-137.
[123] P.J. Aggett, D.J. Atherton, J. More, J. Davey, H.T. Delves, J.T. Harries, Arch Dis Child 55 (1980) 547-550.
[124] T.J. Connors, D.B. Czarnecki, M.I. Haskett, Arch Dermatol 119 (1983) 319-321.
[125] F. Heinen, D. Matern, W. Pringsheim, J.U. Leititis, M. Brandis, European journal of pediatrics 154 (1995) 71-75.
[126] P.H. Parker, G.L. Helinek, R.L. Meneely, S. Stroop, F.K. Ghishan, H.L. Greene, American journal of diseases of children 136 (1982) 77-78.
[127] R.D. Weymouth, R. Kelly, B.J. Lansdell, Aust Paediatr J 18 (1982) 208-210.
[128] A.W. Zimmerman, K.M. Hambidge, M.L. Lepow, R.D. Greenberg, M.L. Stover, C.E. Casey, Pediatrics 69 (1982) 176-183.
[129] A.M. Bye, A. Goodfellow, D.J. Atherton, Pediatr Dermatol 2 (1985) 308-311.
[130] M.T. Glover, D.J. Atherton, Pediatr Dermatol 5 (1988) 10-13.
[131] N. Itsumura, Y. Inamo, F. Okazaki, F. Teranishi, H. Narita, T. Kambe, H. Kodama, PloS one 8 (2013) e64045.
[132] A. Michalczyk, G. Varigos, A. Catto-Smith, R.C. Blomeley, M.L. Ackland, Human genetics 113 (2003) 202-210.
[133] M. Schweigel-Rontgen, Current topics in membranes 73 (2014) 321-355.
[134] J. Jeong, D.J. Eide, Molecular aspects of medicine 34 (2013) 612-619.
[135] L. Huang, S. Tepaamorndech, Molecular aspects of medicine 34 (2013) 548-560.
[136] W. Chowanadisai, B. Lonnerdal, S.L. Kelleher, The Journal of biological chemistry 281 (2006) 39699-39707.
[137] I. Lasry, Y.A. Seo, H. Ityel, N. Shalva, B. Pode-Shakked, F. Glaser, B. Berman, I. Berezovsky, A. Goncearenco, A. Klar, J. Levy, Y. Anikster, S.L. Kelleher, Y.G. Assaraf, The Journal of biological chemistry 287 (2012) 29348-29361.
[138] S. Alam, S.R. Hennigar, C. Gallagher, D.I. Soybel, S.L. Kelleher, Journal of mammary gland biology and neoplasia 20 (2015) 159-172.
[139] L. Qian, B. Wang, N. Tang, W. Zhang, W. Cai, Early human development 88 (2012) 663-668.
[140] Y.A. Seo, S.L. Kelleher, Physiological genomics 42A (2010) 219-227.
[141] L. Kumar, A. Michalczyk, J. McKay, D. Ford, T. Kambe, L. Hudek, G. Varigios, P.E. Taylor, M.L. Ackland, Genes & nutrition 10 (2015) 487.
[142] J.E. Piletz, R.E. Ganschow, Science 199 (1978) 181-183.
[143] M.L. Ackland, J.F. Mercer, The Journal of nutrition 122 (1992) 1214-1218.
[144] D.Y. Lee, N.F. Shay, R.J. Cousins, The Journal of nutrition 122 (1992) 2233-2238.
[145] L.K. Huang, J. Gitschier, Nat Genet 17 (1997) 292-297.
[146] K. Weismann, S. Hoe, L. Knudsen, S.S. Sorensen, Br J Dermatol 101 (1979) 573-579.
[147] P.J. Aggett, D.J. Atherton, H.T. Delves, J.M. Thorn, A. Bangham, B.E. Clayton, J.T. Harries, in: M. Kirchgessner (Ed.), Trace element metabolism in man and animals, Technische Universtat Munchen, Freising-Weihenstephan, 1978, pp. 418-422.
[148] J. Arnaud, A. Favier, Analyst 117 (1992) 1593-1598.
[149] G.W. Wende, J Cutan Dis 20 (1902) 532.
[150] N. Danbolt, K. Closs, Am Derm Venerol 23 (1942) 127-169.
[151] E.J. Moynahan, Lancet 2 (1974) 399-400.
[152] E. Maverakis, M.A. Fung, P.J. Lynch, M. Draznin, D.J. Michael, B. Ruben, N. Fazel, Journal of the American Academy of Dermatology 56 (2007) 116-124.

[153] S. Schmitt, S. Kury, M. Giraud, B. Dreno, M. Kharfi, S. Bezieau, Human mutation 30 (2009) 926-933.
[154] R.K. Chandra, Pediatrics 66 (1980) 789-791.
[155] S. Ozkan, H. Ozkan, E. Fetil, F. Corapcioglu, S. Yilmaz, E. Ozer, Pediatr Dermatol 16 (1999) 444-447.
[156] P. Anttila, O. Simell, S. Salmela, E. Vuori, J Inherit Metab Dis 7 (1984) 46-48.
[157] K.H. Neldner, K.M. Hambidge, New Eng J Med 292 (1975) 879-882.
[158] K. Weismann, N. Kvist, T. Kobayasi, Acta Dermatovener (Stockholm) 63 (1983) 143-146.
[159] P.J. Aggett, H.T. Delves, J.M. Thorn, D.J. Atherton, J.T. Harries, A.D. Bangham, European journal of pediatrics 137 (1981) 23-25.
[160] D. Mack, B. Koletzko, S. Cunnane, E. Cutz, A. Griffiths, Gut 30 (1989) 1426-1429.
[161] M. Garretts, M. Molokhia, The Journal of pediatrics 91 (1977) 492-494.
[162] K. Wang, B. Zhou, Y.-M. Kuo, J. Zemansky, J. Gitschier, Am J Hum Genet 71 (2002) 66-73.
[163] S. Kury, B. Dreno, S. Bezieau, S. Giraudet, M. Kharfi, R. Kamoun, J.-P. Moisan, Nat Genet 31 (2002) 239-240.
[164] S. Kasana, J. Din, W. Maret, Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements 29 (2015) 47-62.
[165] S. Kury, M. Kharfi, R. Kamoun, A. Taieb, E. Mallet, J.J. Baudon, C. Glastre, B. Michel, F. Sebag, D. Brooks, V. Schuster, C. Scoul, B. Dreno, S. Bezieau, J.-P. Moisan, Human mutation 22 (2003) 337-338.

Figure legends:

Fig 1. Zinc-deficient infant born at 37 weeks gestation, showing necrolytic rash at lumbar and anal regions with blistering and desquamation



- Zinc is critical for infant growth and development
- Zinc nutrition depends on zinc bioavailability
- Zinc deficiency is a major global health issue that affects young children
- Alterations in zinc transporters can cause zinc-deficient breast milk