REVIEW

Brazilian studies on zinc deficiency and supplementation: emphasis on children

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Abstract

Objectives: to review the literature of studies developed in Brazil on zinc deficiency and the effects of supplementation.

Methods: a literature review based on bibliographic research was carried out in SciELO, LILACS and MEDLINE/PUBMED databases. A total of 133 studies on zinc deficiency and 116 on the effects of supplementation were identified. Thirty-two articles, 16 of which were observational and 16 interventional, were analyzed.

Results: the studies focused mainly on children (75.0% of the observational and 81.25% of the experimental studies). Biochemical deficiency of zinc in children presented great variability, from 0.0% to 74.3%, with expressive prevalence in most studies. Dietary inadequacy among children presented variability from 16.6% to 46.0%. Five from seven studies showed a positive effect of zinc supplementation on micronutrient nutritional status.

Conclusions: there is evidence of zinc deficiency in children as a public health problem, preventable through micronutrient supplementation.

Key words *Zinc, Nutritional status, Child, Brazil*

Introduction

Zinc is an essential nutrient for human health with numerous structural, biochemical and regulatory functions. Second to iron, zinc is the most abundant micromineral in the human body, found in large quantities in all tissues.[1] It plays crucial roles in cell division, metabolism, sexual development, immunity and cognitive ability, responsible for important structural, catalytic and regulatory actions.[1-3]

Thus, zinc deficiency is associated with negative outcomes such as increased morbidity and mortality, increased severity of infectious diseases, growth deficits, physiological changes (anorexia, hypogonadism, hypogeusia [decreased taste buds], dermatitis, immune system dysfunction, and oxidative and neuropsychological disorders), and impairment of motor and cognitive development.[4]

The genesis of this nutritional deficiency involves multiple etiologies, which include: i) decline of zinc concentrations in breast milk after the first six months of lactation, associated to the low intake of this mineral in complementary feeding, in the case of infants; ii) increased physiological zinc requirements observed in pregnancy, lactation and growth (childhood and adolescence); iii) low animal protein diet, rich in phytates and/or with high energy value; iv) decreased food consumption caused by reduced mobility, which contributes to the reduction of energy needs, dental problems and difficulty of swallowing in the case of the elderly; v) deficiency of other nutrients, such as vitamin A and iron.[5-8]

The World Health Organization/United Nations Children's Fund/International Atomic Energy Agency/International Zinc Consultative Group (WHO/UNICEF/IAEA/IZiNCG) recommend the identification of zinc deficiency as a public health problem from the combined use of three indicators: prevalence of low serum zinc > 20%, prevalence of inadequate dietary zinc intake > 25%, and prevalence of under-five children with height/age deficit > 20%.[9] In this sense, zinc deficiency is considered a global problem. Studies in Latin American countries and the United States of America have shown a variation in average zinc intake between 50% and 80% of the recommended, regardless of age, gender and race. It is suggested that Southeast Asia countries and sub-Saharan Africa are at higher risk of deficiency and that, in other countries, the problem is also relevant, especially in South Asian, Latin American/Central American/Caribbean countries and in the Andean Region.[7,10-13]

However, due to the high costs and logistical problems to obtain biochemical markers of zinc nutritional status, few low-income countries present national data on nutrient status.[12] This implies the importance of developing research to elucidate the need for more specific assessments of zinc deficiency, its etiology and the impact of preventive measures.

Considering these assumptions, the present work aims to review the literature of studies developed in Brazil on zinc deficiency and the effects of supplementation.

Methods

This is a literature review comprising the analysis of observational and experimental studies published between 1990 and 2015. The literature review on the subject was carried out in the following databases: SciELO (Scientific Electronic Library Online), LILACS (Latin American and Caribbean Literature in Health Sciences) and MEDLINE/PUBMED (US National Library of Medicine's - NLM). The bibliographic search was performed on January 28, 2016 by two reviewers. The term "zinc deficiency" was used to search for studies developed in Brazil on zinc deficiency, and the terms “zinc” and “dietary supplementation” were used to find studies developed in Brazil on interventions with zinc in SciELO and LILACS databases. In the case of MEDLINE/PUBMED, "zinc deficiency" and "Brazil" were used to find studies on deficiency, and "zinc" , "dietary supplementation" and "Brazil" to studies on effects of zinc supplementation.

After studies were identified in the three databases, the process of exclusion was started in one of them, without quantification. Similarly, in the case of studies involving the same population and sample, only one study was considered. For calculation of the total number of studies identified, duplication in the databases was checked, and each article was counted only once.

The decision on article inclusion comprised two steps: i) screening by reading titles and abstracts, ii) reading articles in full-length. In the screening phase, studies with the following characteristics were eliminated: thesis/dissertation, literature review, studies not performed with humans and developed with non-Brazilian population groups. In the full-length reading phase, articles with Brazilian participants of any age group and studies with observational and experimental approach were selected. The following exclusion criteria were used: studies with individuals with any kind of non-infectious disease or surgical/invasive procedures or with special characteristics (sportsmen), observational studies without a diagnosis of zinc nutritional status through the use of biochemical/dietary indicators (in the case of studies on zinc deficiency), observational studies (in the case of studies on zinc intervention effects), experimental studies (in the case of studies on zinc deficiency), experimental studies not including zinc supplementation (in the case of studies on zinc intervention effects).

Observational articles were characterized according to author and year of publication, target group of study, methods employed to diagnose zinc deficiency and main results. Experimental articles were characterized according to author and year of publication, target group of study, methods employed to diagnose zinc deficiency, type of intervention evaluated and main results.

The quality of the studies was assessed by means of a checklist adapted from the Downs and Black criteria.[14] Articles were analyzed based on: (1) quality of description of objectives; (2) quality of description of the study outcome (observational and experimental studies) and intervention outcome (experimental studies); (3) quality of sample characterization (description of participants and eligibility criteria); (4) quality of description and discussion of the main confounding factors, as well as masking in the experimental studies; (5) quality of description of loss of participants; (6) quality of description of the main results of the study; (7) proof of the representativity of the sample studied in relation to the study population; (8) description of sample and sample calculation (observational studies) or randomization (experimental studies); (9) accuracy of instruments used to measure the outcome; (10) adequacy of statistical tests used to characterize variables; (11) adequacy of the evaluation method to compare groups (equal follow-up periods in cohort and experimental studies, equal time periods between exposure and outcome in control case studies); (12) adequacy of comparative groups (recruited from the same population and in the same period of time); (13) adequacy of fit of confounding factors.

The evaluation of each article was performed by assigning the score 1 when the quality criterion was met and the score 0 when the evaluation was negative. At the end, to evaluate the quality of each article, scores were summed and, based on this sum, the articles were classified into the categories: high quality, when total score was between 9 and 13; average quality, when total score was between 6 and 8; low quality, when total score was less than or equal to 5.

During all stages, the two reviewers worked independently. The extracted data were crossed to verify agreement. Discordant results were resolved by consensus.

Results

Initially, 133 studies on zinc deficiency and 116 on effects of nutrient interventions were identified. The results of the identification and selection of studies are presented in the flowchart of the review in Figure 1.

As for the quality evaluation of the studies (data not presented in tables), 16 were categorized as having average quality (12 observational and 4 experimental) and 16, high quality (4 observational and 12 experimental). The quality criteria in which articles presented the greatest limitation were, in particular, proof of representativeness of the sample studied in relation to the study population (in observational and experimental studies); definition of main confounding factors (in observational studies) and description of loss of participant (in observational and experimental studies). Considering that all the articles had an average or high quality and that the main risks of bias were associated with the analysis of loss of participants and confounding factors, without negative effects on the objectives of the review, we decided to systematize all the studies

The analysis of sample representativeness indicates that 15 studies[16,17,19,20,29,31,34,36,38-40,42,44-46] used a representative sample and random selection of participants, five[15,18,21,22,37] studied a large population percentage and ten[23,24,26,27,30,32,33,35,41,43] studied populations with no characteristic of representativeness. With the exception of two studies,[25,30] representativeness was guaranteed in all others that focused on preschool children (Tables 1 and 2).

Observational studies (Table 1) show great diversity as age group/physiological state, study population, diagnostic methods and association with functional indicators. Children were the most frequently studied group (n = 12).[15,16-23,25,29,30] The Southeast Region concentrated most of the studies (n = 10),[18,19,21-27,30] while the other regions had a maximum of four studies. The most commonly used biochemical indicators of zinc nutritional status were plasma zinc (n = 6),[15,18,24,27,28,30] serum zinc (n=5)[17,19,21-23] and erythrocyte zinc (n = 3).[15,20,23] In order to evaluate dietary zinc intake, the 24-hour recall was the most commonly used instrument. The association of zinc nutritional status with growth, childhood infectious diseases and status of other

Figure 1

Flowchart of phases of the review of Brazilian studies on zinc deficiency and the effects of supplementation. 1990 to 2015.

Number of records identified in databases (28/01/2016)

	Deficiency	Effects
- SciELO:	43	13
- LILACS:	33	19
- Medline/Pubmed:	84	97

Number of duplicated records that were eliminated

Deficiency	Effects
27	13

Number of non-replicated records submitted to screening

Deficiency	Effects
133	116

Number of records eliminated (screening phase)

	Deficiency	Effects
- thesis/dissertation:	03	01
- review articles:	09	08
- studies not performed with humans:	48	46
- studies performed with non-Brazilian population groups:	02	02

Number of non-replicated records analyzed to decide on their eligibility

Deficiency	Effects
71	59

Number of records eliminated (full-length reading phase)

	Deficiency	Effects
- studies on non-infectious disease or surgical/ invasive or special features:	23	22
- studies without a diagnosis of the nutritional zinc status:	18	-
- observational studies:	-	08
- experimental studies:	14	-
- studies not including isolated zinc supplementation:	-	13

Total number of articles included in the review

Deficiency	Effects
16	16

Table 1

Synthesis of observational manuscripts on zinc deficiency in Brazil. 1990 to 2015.

Author, year	Target group	Diagnostic methods	Main results (prevalences and associations)
Jardim-Botelho *et al.*,[15] 2015	153 children, 2 to 11 months old, born at term, living in areas of social vulnerability of Laranjeiras, SE	Biochemical evaluation: plasma zinc, erythrocyte zinc	- Plasma zinc deficiency: 58% - Erythrocyte zinc deficiency: 67% - Significantly lower plasma zinc concentrations in normal weight children - There was no statistical difference between erythrocyte zinc concentrations and E/I index
Garcia *et al.*,[16] 2011	164 children, aged 6 to 24 months, living in the urban area of Acroelândia, AC	Dietary assessment: food consumption by food history	-Inadequate dietary intake of zinc: 46%
Figueroa Pedraza *et al.*,[17] 2011	235 children, aged 6 to 72 months, assisted in day care centers in the State of Paraíba	- Biochemical evaluation: serum zinc - Dietary assessment: food consumption through 24-hour recall	- Zinc deficiency: 16.2% - Inadequate dietary intake of zinc: 16.6% - Mean zinc concentrations significantly lower in children of low weight mothers than in children of normal weight mothers - There was no statistical difference between serum zinc concentrations according to dietary zinc adequacy, height-for-age (H/A) index, and variables related to children's biological characteristics, infant feeding, family history and socioeconomic conditions
Beinner [18], 2010	176 children, aged 6 to 24 months, living in a rural area of Diamantina, MG	-Biochemical evaluation: plasma zinc, zinc in hair - Dietary assessment: food consumption through 24-hour recall	- Plasma zinc deficiency: 11.2% - Zinc deficiency in hair: 16.8% - Inadequate dietary intake of zinc: 30.6% - There was no statistical difference between zinc deficiencies in plasma and hair, according to sex - Absence of correlation between plasma zinc concentrations, zinc content in hair, anthropometric indices (W/A, H/A, W/H) and dietary zinc intake
Custodio *et al.*,[19] 2009	103 children, 5.5 to 11 months old, assisted at a health unit in Ribeirão Preto, SP	Biochemical evaluation: serum zinc	- Zinc Deficiency: 0% - Lack of statistical association between serum zinc concentrations and vitamin A deficiency
Costa *et al.*,[20] 2008	239 children, aged 3 to 6 years, assisted in day care centers in Teresina, PI	Biochemical evaluation: erythrocyte zinc	- Zinc Deficiency: 74.3% - Absence of statistical association between serum zinc concentrations and anthropometric indices (W/A, H/A, W/H)

* Results on the prevalence of zinc deficiency with the use of biochemical indicators and/or prevalence of dietary inadequacy of dietary zinc not available in the articles; H/A = Height-for-age; W/H = Weight-for-height; W/A = Weight-for-age.

continue

Table 1 **continuation**

Synthesis of observational manuscripts on zinc deficiency in Brazil. 1990 to 2015.

Author, year	Target group	Diagnostic methods	Main results (prevalences and associations)
Borges *et al.*,[21] 2007	104 children, aged 1 to 5 years, living in the urban area of Duque de Caxias, RJ	Biochemical evaluation: serum zinc	- Zinc Deficiency: 7.5% - Assessment of statistical association between serum zinc concentrations and anthropometric indices (W/A, H/A) - Mean zinc concentrations significantly lower in children with diarrhea than those without reported diarrhea
Ferraz *et al.*,[22] 2007	182 children, aged ≥ 2 years and < 6 years, assisted at the Social Medical Center and Community of Vila Lobato, Ribeirão Preto, SP	Biochemical evaluation: serum zinc	- Zinc Deficiency: 0.5% - Lack of correlation between serum concentrations of zinc and retinol - Lack of correlation between serum zinc concentrations in males and females - Children aged ≥ 48 to <60 months had lower serum zinc concentrations than children of other ages - Concentrations of serum zinc did not change due to diarrhea and/or fever episodes
Santos *et al.*,[23] 2007	86 schoolchildren, aged 7 to 15 years, living in two favelas (Rocinha and Beira Rio) in the city of São Paulo, SP	Biochemical evaluation: serum zinc	- Zinc deficiency: 8.14% - Mean concentrations of zinc without significant difference according between sexs and non-correlated to presence of anemia
Maia *et al.*,[24] 2007*	73 female adolescents, from 14 to 18 years of age, Health centers of Rio de Janeiro, RJ	- Biochemical evaluation: plasma zinc, erythrocyte zinc, alkaline phosphatase, metallothionein, superoxide dismutase - Dietary assessment: food consumption through 24-hour recall	- Inadequate dietary intake of zinc (pregnant adolescents): 67% - Inadequate dietary intake of zinc (non-pregnant and non-lactating adolescents): 78% - Inadequate dietary intake of zinc (lactating adolescents): 77% - Concentrations of plasma zinc in pregnant adolescents were lower than that of non-pregnant and non-lactating adolescents, and of lactating adolescents - Concentration of erythrocyte zinc did not differ between pregnant adolescents, non-pregnant and non-lactating adolescents, and lactating adolescents - Significant correlation between erythrocyte zinc and metallothionein levels in non-pregnant and non-lactating adolescents and lactating adolescents, a fact not observed in pregnant adolescents - Significant correlation between alkaline phosphatase and plasma zinc concentrations between metallothionein and plasma zinc concentrations and between concentrations of superoxide dismutase and erythrocyte zinc in non-pregnant and non-lactating adolescents, a fact not observed in pregnant adolescents and lactating adolescents

* Results on the prevalence of zinc deficiency with the use of biochemical indicators and/or prevalence of dietary inadequacy of dietary zinc not available in the articles; H/A = Height-for-age; W/H = Weight-for-height; W/A = Weight-for-age.

continue

Table 1 **continuation**

Synthesis of observational manuscripts on zinc deficiency in Brazil. 1990 to 2015.

Author, year	Target group	Diagnostic methods	Main results (prevalences and associations)
Tremeschin *et al.*,[25] 2007*	40 preschool children, distributed in three groups according to AIDS-related characteristics, living in the city of Ribeirão Preto, SP	Dietary assessment: food consumption by frequency of consumption	- Dietary zinc intake without statistical difference between HIV-positive children, HIV-negative children born to infected mothers and HIV-negative children
Morimoto *et al.*,[26] 2006	119 students, aged 19 to 30, from a public university in the State of São Paulo	- Dietary assessment: food consumption per non-consecutive 3-day record	- Inadequate dietary zinc intake: 47%
Cesar *et al.*,[27] 2005*	80 elderly assisted at the Araraquara Rehabilitation Center, SP	- Biochemical evaluation: plasma zinc - Dietary assessment: food consumption through 24-hour recall and frequency of consumption	- Mean concentrations of plasma zinc below the references for age in both men and women - Mean dietary zinc intake according to normality patterns in both men and women - Lack of correlation between dietary intake of zinc and plasma zinc - Significant correlation between dietary intake of zinc and energy and protein intake in women, a fact also observed in men for protein intake - Meats provided 68% of total zinc in the case of women and 78% in the case of men
Weyenbergh *et al.*,[28] 2004	31 individuals with leishmaniasis and 25 controls of endemic and non-endemic areas, living in the rural district of Corte da Pedra, Bahia	- Biochemical evaluation: plasma zinc	- Zinc Deficiency (total): 25.8% - Zinc Deficiency (with visceral leishmaniasis): 70% - Zinc deficiency (carriers of mucosal leishmaniasis): 14.2% - Zinc Deficiency (carriers of localized cutaneous leishmaniasis): 0% - Zinc Deficiency (Controls): 0% - Lower plasma levels of zinc in leishmaniasis patients compared to controls

* Results on the prevalence of zinc deficiency with the use of biochemical indicators and/or prevalence of dietary inadequacy of dietary zinc not available in the articles; H/A = Height-for-age; W/H = Weight-for-height; W/A = Weight-for-age.

continue

Table 1

conclusion

Synthesis of observational manuscripts on zinc deficiency in Brazil. 1990 to 2015.

Author, year	Target group	Diagnostic methods	Main results (prevalences and associations)
Marinho e Roncada,[29] 2002	370 children, 3 to 6 years old, living in three capitals of the Western Amazon: Boa Vista (n = 54), Manaus (n = 238) and Porto Velho (n = 78)	Dietary assessment: food consumption through 24-hour recall and frequency of consumption	-Inadequate dietary intake of zinc (total): 27.2% -Inadequate dietary intake of zinc (Boa Vista): 16.3% -Inadequate dietary intake of zinc (Manaus): 30.3% -Inadequate dietary intake of zinc (Porto Velho): 25.5% - The mean daily consumption of zinc in Boa Vista, Manaus and Porto Velho was 8.4 (± 2.0) mg, 6.9 (± 1.7) mg and 7.4 (± 1.8) mg , respectively -16.7%, 19.8% and 18.0% of the children of Boa Vista, Manaus and Porto Velho, respectively, consumed less than 50% of the daily recommendations of zinc
Fávaro *et al.*,[30] 1990	126 children, aged 2 to 7 years, living in three peripheral districts of Ribeirão Preto, SP	Biochemical evaluation: plasma zinc	- Zinc Deficiency: 13% - Lack of statistical difference between the prevalence of zinc deficiency in girls (14%) and boys (11.7%) - Absence of statistical association between serum zinc concentrations and anthropometric indices (W/H, tricipital fold, brachial circumference)

* Results on the prevalence of zinc deficiency with the use of biochemical indicators and/or prevalence of dietary inadequacy of dietary zinc not available in the articles; H/A = Height-for-age; W/H = Weight-for-height; W/A = Weight-for-age.

Table 2

Synthesis of experimental manuscripts on the functional and nutritional effects of micronutrients of zinc interventions in Brazil. 1990 to 2015.

Author, year	Target group	Diagnostic methods	Tipe of intervention	Main results (intervention effects)
Lima *et al.*,[31] 2013	167 children, aged 3 months to nine years, with short stature, living in favelas in Fortaleza,CE	No evaluation	Supplementation alone or combined with zinc, vitamin A and glutamine	- Significantly higher verbal learning scores in female children supplemented with zinc, vitamin A and glutamine than those supplemented with zinc and vitamin A and those receiving placebo alone
Moura *et al.*,[32] 2013	36 children, aged 6 to 9 years, from Natal, RN	Biochemical evaluation: serum zinc	Zinc suplementation	- Significant improvement in Verbal Intelligence Quotient and in Intelligence Quotient Performance after supplementation
Alves *et al.*,[33] 2012	30 children, aged 6 to 9 years, enrolled in schools in the city of Natal, RN	Biochemical evaluation: serum zinc	Supplementation with zinc *versus* intravenous zinc administration	- Significant increase in serious zinc levels during intravenous administration of zinc and after supplementation - Significant increases in plasma concentrations of GH Growth Hormone during intravenous administration of zinc - Significant increase in plasma concentrations of IGF-1-like Growth Factor and IGFBP3 Insulin-Like Growth Factor Binding Protein 5 after supplementation - Significant increase in weight and consumption of energy, protein, carbohydrate, calcium, iron and zinc after supplementation - Positive correlation between the areas under the curve of Growth Hormone GH and zinc after supplementation
Mitter *et al.*,[34] 2012	213 children, aged 2 months to 9 years, with short height, living in favelas in Fortaleza, CE	No evaluation	Supplementation alone or combined with zinc, vitamin A and glutamine	- Improvements in the lactulose/mannitol ratio in children with apolipoprotein E positive and apolipoprotein E negative genotype after supplementation with vitamin A, zinc and glutamine - No significant differences in the anthropometric indices (W/A, H/A, W/H) between groups
Marreiro *et al.*,[35] 2006	56 obese women, aged 25 to 45, from São Paulo	Biochemical evaluation: plasma zinc, urinary zinc, erythrocyte zinc	Suplementation with zinc *versus* placebo	- Lack of statistically significant difference between groups in relation to anthropometric and body composition parameters, fasting glycemia, leptin concentrations, and plasma and erythrocyte zinc concentrations - Significant increase in urinary zinc concentration in supplemented women - Significant reduction of insulin concentrations and the Homeostasis Assessment Model Index in supplemented women

H/A = height-for-age; W/A = weight-for-age; W/H = weight-for-height.

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Table 2

Synthesis of experimental manuscripts on the functional and nutritional effects of micronutrients of zinc interventions in Brazil. 1990 to 2015.

Author, year	Target group	Diagnostic methods	Tipe of intervention	Main results (intervention effects)
Silva *et al*.,[36] 2006	58 children, aged 12-59 months, participating in the Governmental Program to Combat Nutritional Deficiencies, living in the city of São Sebastião, DF	Biochemical evaluation: serum zinco	Zinc suplementation *versus* placebo	- Height and weight growth evolution after supplementation in both groups, but without statistical difference between them - Significant difference in zinc and iron concentrations after supplementation, with higher mean values in the supplemented group
Campos Júnior *et al*.,[37] 2004	40 under-five children, with lack of appetite for salt meals, assisted at the University Hospital of Brasília, DF	No evaluation	Zinc suplementation *versus* placebo	-The recovery of appetite for salt meals was significantly higher in children supplemented with zinc than in the placebo group
Al-Sonboli *et al*.,[38] 2003	74 children younger than 3 months to 60 months, with acute diarrhea, assisted at emergency services in Aracaju, SE	Biochemical evaluation: serum zinc	Zinc suplementation *versus* placebo	- Significant reduction in the number of days with diarrhea and liquid stools, number of evacuations, and number of days of hospital stay in the group of children supplemented with zinc, when compared to the placebo group
Chen P *et al*.,[39] 2003	75 children, aged 2 to 97 months, living in the urban area of Fortaleza, CE	Biochemical evaluation: serum zinc	Supplementation with vitamin A *versus* zinc	- Lack statistically significant difference between serum zinc concentrations and children's age - There was a significant increase in the H/A index after supplementation
Cuevas *et al*.,[40] 2002	98 children, younger than 15 years, exposed to adults with smear-positive pulmonary tuberculosis, Aracaju, SE	No evaluation	Zinc suplementation *versus* placebo	- The mean diameter of the hardening area observed in the tuberculin test was significantly higher in children supplemented with zinc than in the placebo group, regardless of the nutritional status evaluated by W/A, H/A, W/H indices

H/A = height-for-age; W/A = weight-for-age; W/H = weight-for-height.

continue

conclusion

Table 2

Synthesis of experimental manuscripts on the functional and nutritional effects of micronutrients of zinc interventions in Brazil. 1990 to 2015.

Author, year	Target group	Diagnostic methods	Tipe of intervention	Main results (intervention effects)
Donangelo *et al*.,[41] 2002	23 women, aged 20 to 28 years, with low iron stores, but without anemia, from Rio de Janeiro, RJ	Biochemical evaluation: plasma zinc, erythrocyte zinc, urinary zinc	Zinc suplementation *versus* iron	- Increase of plasma, erythrocyte and urinary zinc concentrations after zinc supplementation - Absence of effect on plasma, erythrocyte and urinary zinc concentrations after iron supplementation
Porto *et al*.,[42] 2000	18 children, aged 7 to 10 years, with short height, from Rio de Janeiro, RJ	Biochemical evaluation: plasma zinc	Zinc suplementation *versus* placebo	- Significant increase in growth rate during zinc supplementation that did not persist after discontinuation
Castro *et al*.,[43] 1999	15 healthy men, with a mean age of 23 years, from São Paulo, SP	Biochemical evaluation: plasma zinc	Supplementation with zinc *versus* placebo and intravenous administration of zinc *versus* placebo	- Significant increase in serum zinc concentrations after oral supplementation and intravenous administration - Lack of effect related to prolactin and thyrotropin-releasing hormone response
Ashworth *et al*.,[44] 1998	205 newborns with low birth weight, born in a hospital in Pernambuco	No evaluation	Supplementation with 1 mg of zinc *versus* 5 mg of zinc versus placebo	- Absence of significant difference in the mental and psychomotor development scores between groups, after 6 and 12 months of supplementation - Newborns who received 5 mg of zinc showed better behavioral performance than the other groups after 12 months of supplementation
Lira *et al*.,[45] 1998	134 newborns, from birth to 26 weeks of age, from Pernambuco	Assessment of zinc-rich food consumption	Supplementation with 1mg of zinc *versus* supplementation with 5mg of zinc *versus* placebo	- Newborns who received 5 mg of zinc showed lower prevalence of diarrhea and cough - Significant effect of zinc supplementation on immune function, occurrence of vomiting, fever, loss of appetite and growth
Marinho *et al*.,[46] 1991	471 pre-school children with Ascaris lumbricoides and/or Giardia lamblia enrolled in schools or day care centers in a poor neighborhood of Manaus, AM	Biochemical evaluation: zinc in hair	Supplementation with vitamin A and/or zinc *versus* placebo	- Significant effect of antiparasitics and supplementation on serum retinol levels

H/A = height-for-age; W/A = weight-for-age; W/H = weight-for-height.

micronutrients was addressed in six,[15,17,18,20,21,30] two[21,22] and three[19,22,23] studies, respectively. Considering the group of children, six studies[18,19,21,22,25,30] were performed in the Southeast, eight[15,17-22,30] showed results of zinc deficiency prevalence using biochemical parameters, and five[16-18,25,29] presented results of zinc dietary inadequacy.

Prevalence of zinc dietary inadequacy was high in all groups studied. There was a variation of inadequacy from 16.6% to 46.0% in children. Results found by Maia *et al*.[24] showed high frequencies when evaluating three groups of adolescents (pregnant, lactating, non-pregnant and non-lactating). This study also found lower concentrations of plasma zinc in pregnant adolescents when compared with the other two groups of adolescents, a fact that was not observed when considering the nutritional zinc status by erythrocyte concentrations.

Prevalence of biochemical zinc deficiency in children ranged from 0%[19] to 74.3%.[20] Prevalence of 0%[19] and 0.5%[22] were found in studies conducted in Ribeirão Preto, SP. The highest prevalence was found in Teresina,[20] Northeast Region of Brazil. In other populations, prevalence of zinc deficiency showed more similar values, ranging from 7.5%[21] to 16.8%.[18] The prevalence found in school children living in two poor communities (favelas) in São Paulo was 8.14%.[23]

Only three studies[15,17,21] reported some statistical association with the outcomes of interest. These investigations, developed with children, indicated: i) significantly lower plasma zinc concentrations in normal-weight children compared to those obese or at risk of obesity;[15] ii) significantly lower mean serum zinc concentrations in children born to low weight mothers than in children born to normal weight mothers; (iii) significantly lower mean serum zinc concentrations in children with diarrhea than in children without diarrhea.

Correlation between different biochemical indicators of zinc nutritional status was analyzed in three articles.[18,24,27] Only one study presented results with statistical significance,[24] found between: i) erythrocyte zinc and metallothionein concentrations in non-pregnant adolescents and (ii) alkaline phosphatase and plasma zinc concentrations, metallothionein and plasma zinc concentrations, and superoxide dismutase and erythrocyte zinc concentrations in non-pregnant and non-lactating adolescents. Significant statistical association between dietary intake of zinc and energy and protein intake was indicated in the elderly.[27]

According to Table 2, the impact on growth, development and improvement of nutritional status of micronutrients was considered in five,[34,36,39,42,45] three,[31,32,44] and seven studies,[33,35,36,39,41,43,46] respectively, out of 16 experimental studies.[31-46] The hypothesized effect of zinc supplementation on growth was confirmed in children living in an urban area of Fortaleza, CE,[39] and in schoolchildren of short heigth in Rio de Janeiro.[42] The three studies[31,32,44] showed a positive effect on development, according to the indicators used by the researchers. The effect of zinc supplementation on the nutritional status of micronutrients was found in six[33,35,36,41,43,46] of the studies with suchlike analyses, of which five studies[33,35,36,41,43] reported the effect on zinc nutritional status.

Discussion

Results of the present study show the existence of isolated experiments related to the evaluation of zinc nutritional status in Brazil. The scarcity of studies with representative population sample and heterogeneity regarding objectives, study population, geographic analysis units and diagnostic methods make it difficult to synthesize the data so as to estimate the magnitude and etiology of zinc deficiency in Brazil in different population groups. This situation warns of the need for new and more comprehensive research on zinc deficiency in Brazil. Prior knowledge suggests nutritional deficiency among children.[15,17,18,20,30] It was also observed that experimental studies[31-46] have prioritized the analysis of zinc intervention effects on the nutritional status of micronutrients,[33,35,36,39,41,43,46] but present limitations in the analysis of other outcomes, such as functional parameters.

Despite the previous restrictions, it was possible to verify expressive prevalence of dietary inadequacy in all the studies, above 25% in most of them, a value indicated by the IZiNCG[47] as indicative of high risk of zinc deficiency. This result converges with the risk of dietary inadequacy of zinc for the Brazilian population (20.3%),[7] which was estimated from the national availability of zinc-rich food and the bioavailability of zinc in food sources. This value is closer to the world estimate (17.3%) than to that of South America (6.4%),[12,48] and denotes the problem of zinc deficiency in the country, also suggested by the results systematized here.

Children also stand out as the most frequently studied subjects. In this group, zinc biochemical deficiency above 10%, which represents a moderate public health problem according to IZiNCG,[9,49] was found in five (55.5%)[15,17,18,20,30] of the nine studies.[15,17,18-23,30] Furthermore, dietetic inadequacy of dietary zinc above 25% was found in the three studies (100%)[16,18,29] that presented such results. Thus, on the basis of dietary and biochemical indicators, zinc deficiency among children is indicated as an important public health problem.

Also in the context of the reviewed observational studies, limited reports of statistical associations make it impossible to systematize the etiological factors of zinc deficiency. Despite of this, it is worth considering that nutritional deficiencies share a context of poverty, low levels of education and other unfavorable social factors, which are associated with food insecurity in families, inadequate maternal and child care, inadequate health services and unhealthy environment.[50] It is therefore, important to analyze socioeconomic (maternal education, income, employment, access to health services, environmental sanitation) and biological (age, reproductive cycle, presence of diseases) factors to identify vulnerable groups to zinc deficiency.[7]

Lack of research on zinc nutritional status found in this study may be based on technical difficulties related to obtaining the sample, laboratory analysis and interpreting results.[51] Evidence shows that zinc concentrations can vary up to 20% within a period of 24 hours, mainly due to food intake. There is an immediate increase after meals and a progressive reduction in the following four hours. During nighttime fasting, serum concentration increases, so that the highest levels of the day are usually seen in the morning. Diurnal variations were also observed in fasting subjects, with decreases in concentrations in the morning to mid-afternoon, followed by a progressive increase to levels similar to those initially verified. Thus, reduced concentrations of serum zinc can occur in physiological response and are not necessarily indicative of low status of this mineral. Serum zinc values below normal levels may occur due to the presence of other factors, such as acute infections and inflammation, hypoalbuminemia, hemolysis and hemodilution.[7]

There is no validated instrument for assessing the adequacy of zinc nutritional status.[52] Such evaluation is difficult because of the fact that not all the zinc ingested in food is used by the organism, since its bioavailability may be affected by the process of intestinal absorption or blood circulation. Intestinal absorption may be reduced by antagonistic factors in the diet, such as phytate, oxalate, tannins and polyphenols; whereas in the circulation, zinc may compete with copper and iron, depending on the amount of these elements in the bloodstream.[10]

A more precise characterization of the magnitude and distribution of zinc deficiency precludes the minimization of the previous barriers or the standardized adoption of the currently recommended evaluation methods. In this sense, the IZiNCG recommends the use of serum zinc concentrations and the 24-hour recall,[7] which were the method most used by the authors.

Regarding intervention studies, the studies demonstrated the importance of zinc supplementation to the nutritional status of zinc itself. This statement is important considering the synergistic effects of zinc, iron and vitamin A, and the coexistence of deficiencies.[50] Despite the scientific evidence that iron can inhibit zinc absorption, contrary to the positive effect of the vitamin A,[53] the results of this review seem to indicate that the nutritional status of zinc may be benefited by the micronutrient supplementation regardless the iron and vitamin A nutritional situation.

As for growth and development, the limited number of studies on growth and the asymmetries of their results make it impossible to support hypotheses on the impact of zinc supplementation on these functional parameters.

We call attention to the fact that these results may be due to the differential effect of zinc supplementation on linear growth, depending on whether it is used alone or in combination with other micronutrients and/or other factors such as dose and time of supplementation.[1,53] A systematic review focusing on research in Latin American countries also found a lack of research on the theme and suggested that zinc supplementation has no significant impact on linear growth, an effect that would be found in cases of zinc deficient children associated with other nutritional deficiencies.[54]

However, it should be noted that important positive effects in growth and development have been attributed to zinc, considering the benefits this mineral provides to general health, with emphasis on hormonal regulation (as growth hormone), brain functionality, immune system integrity, and prevention and control of a wide range of infectious and chronic diseases.[1,4,55]

In the present review, relying only on supplementation experiences hampers any attempt to synthesize the comparative effects of interventions that could be used to prevent zinc deficiency. This gap deserves attention, due to its implications on relevant issues such as interaction of zinc with other micronutrients, competitive processes related to zinc absorption, and implicit advantages of interventions with nutrients related to the way they are consumed (food fortification facilitates the integration to the usual diet and offers the possibility of an additional source of energy and high-quality protein).[53,56,57] Despite the evidence indicating food fortification as a low-cost intervention to correct zinc deficiency,[58] the results presented indicate that these interventions have been poorly tested in Brazil and may restrict decisions on preventive interventions aimed at reducing zinc deficiency and its consequences.

The main contribution of this review refers to zinc deficiency as an important public health problem among Brazilian children that can be prevented through micronutrient supplementation. The relevance of these findings comes not only from the implications for health, development and disease prevention in the group of children who composed this review.[1,4] Recent scientific evidence also suggests that low levels of zinc may be associated with obesity,[59] which represents another worrying epidemiological situation among Brazilian children.[60]

This review, in particular, presented some limitations, namely, the inclusion of articles identified in only three bibliographic bases, with search terms that could be more comprehensive, which restricted the spectrum of the analysis. Nevertheless, the relevance of the results obtained should be highlighted considering the lack of systematized data on zinc deficiency and the effects of interventions with the nutrient, based on studies developed with populations in Brazil. In this sense, the results presented reinforce the need to plan and develop studies with representative samples, with feasible replication, using the same covariables and exposure categories, for similar geographic units.

Also, although the reviewed papers stand out for their quality, the design of future studies should focus on the loss of participants and on the confounding factors, which are the main negative aspects of the validity of studies identified in the review. From the diagnostic point of view, it is fundamental to use biomarkers that more accurately reflect zinc levels in the body, associated with validated dietary instruments for the study population. In the context of experimental design research, it is worth mentioning that the lack of diagnosis in five of the reviewed studies impairs knowledge about the nutritional zinc status in the studied children and its distribution according to characteristics of interest.

In conclusion, despite the epidemiological and clinical impact, as well as its importance in all phases of life, Brazilian studies on zinc nutritional status are insufficient. The results allow the composition of a preliminary picture on the dietary inadequacy of zinc, zinc deficiency as a public health problem among children and the positive impact of zinc supplementation on the nutritional status of this micro-nutrient.

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