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ORIGINAL ARTICLE

The association of serum levels of zinc and vitamin D with wasting among Iranian pre-school children

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Abstract

Purpose Wasting is a main indicator of Child's undernutrition that is associated with several non-communicable diseases and child mortality. This is the first population-based study which evaluated the association of serum zinc and vitamin D levels with wasting in a Middle East region. We also reported the prevalence of vitamin D and zinc deficiencies among Iranian pre-school children aged 6 years.

Methods This was a multicenter cross-sectional study that included 425 children aged between 5 and 7 years (on average 6 years) with BMI-for-age *Z*-scores of < -1 SD resident in urban and rural areas of Iran in the spring of 2012 as part of the National Integrated Micronutrient Survey 2 (NIMS-2). Anthropometric measurements and blood sampling were obtained. The prevalence of vitamin D and zinc deficiencies together with the correlations of these variables with the increase of BMI-for-age *Z*-scores were evaluated.

Results The prevalence of vitamin D and zinc deficiencies was 18.8% and 12.7%, respectively. In addition, 31.1% of children were wasted. Children in the second tertile of 25(OH)D levels were less likely to have wasting compared with those in the first tertile in both crude and adjusted models (OR 0.47, 95% CI 0.27–0.83). A significant inverse association was found between serum levels of zinc and wasting (OR 0.57, 95% CI 0.34–0.96); such that after adjusting for confounders, children in the highest tertile of serum zinc had 47% less odds of wasting compared with those in the first tertile (OR 0.53, 95% CI 0.31–0.91).

Conclusion The prevalence of vitamin D and zinc deficiencies among Iranian pre-school children aged 6 years was 18.8 and 12.7%, respectively. Serum levels of vitamin D and zinc were inversely associated with wasting either before or after controlling for confounders.

Level of evidence Level III, case–control analytic studies.

Keywords Malnutrition · Vitamin D · Zinc · Wasting · Children

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Introduction

Wasting from malnutrition, defined as low weight for height, is a major public health problem among children and is associated with growth retardation, school performance problems, and even child mortality particularly in developing countries [1–3]. It has been estimated that 52 million pre-school children are engaged in wasting worldwide, contributing to approximately 800,000 child death annually [4, 5]. The prevalence of wasting in Asian nations is higher than that in western countries [6]. National estimates reported a prevalence of 7.9% among Iranian children [7]. Wasting imposes a high cost to the health care system and is associated with several chronic diseases such as diabetes mellitus and cardiovascular diseases later in adulthood [8–11].

The global prevalence of vitamin D deficiency is increasing at an alarming rate [12, 13]. A recent study reported vitamin D deficiency in 12.4% of Tajik children with the age of 6–59 months [14]. Sporadic studies in Iran have indicated the high rates of vitamin D deficiency among various age groups [15–18]. Advances in the biology of vitamin D revealed an extended role of vitamin D far beyond calcium–phosphorus hemostasis conferring potential therapeutic role in several diseases, such as type 1 diabetes mellitus, multiple sclerosis, and obesity [19]. Zinc deficiency is among the top ten contributing factors to the burden of disease in developing countries [20]. Zinc deficiency among children was reported to be four times more prevalent than iron deficiency [21]. A moderate zinc deficiency of 5–30% was reported among children and adolescents of different countries [22]. However, earlier studies have mainly focused on infants or adolescence, and data on the prevalence of zinc and vitamin D deficiencies among pre-school children are scarce.

Several risk factors including genetic and environmental factors have been suggested for child wasting [19–26]. Among environmental factors, great attention is given to the infection, diet, and malnutrition [23, 27–29]. Earlier studies have shown that micronutrient deficiencies including zinc and vitamin D deficiencies are associated with increased risk of stunting among children [30–33]; however, the associations with wasting are less studied. Some studies reported that serum levels of zinc and vitamin D were inversely associated with wasting [30, 34], while others failed to find any significant relationship [14, 35, 36]. Therefore, data in this regard are conflicting. Moreover, most studies on the association between serum level of vitamin D and wasting came from non-Middle Eastern countries where the prevalence of micronutrient deficiencies and wasting is estimated to be high [30, 33, 35]. Overall, the current study was aimed to examine the association of serum zinc and vitamin D levels with wasting among pre-school children in the Middle East.

Materials and methods

Participants

This was a cross-sectional study conducted within the framework of the National Integrated Micronutrient Survey 2 (NIMS-2). The survey was performed in urban and rural areas of Iran in the spring of 2012. This study was conducted by the School of Nutritional Sciences and Dietetics (SNSD), Tehran University of Medical Sciences (TUMS), Tehran, Iran. Details on sampling and data collection methods were published previously [37]. Briefly, in NIMS-2, all provinces in Iran were divided into 11 major zones. Then, each zone was divided into 80 clusters. In total, 880 clusters (530 urban and 350 rural) with representative sequences were determined across Iran. Five subjects were randomly selected from each cluster for each age group (toddlers, pre-school children, adolescences, adults, pregnant women). Overall, 4400 subjects were included for each age group. In the present study, we only focused on pre-school children aged between 5 and 7 years (on average 6 years). Iranian children who were referred to the urban health units or rural health houses to receive primary health care services were included in the study. We excluded those who consumed vitamin D and zinc supplements. A total of 425 children with complete data on demographic variables, laboratory and anthropometric measures were included in the final analysis. Written informed consent was obtained from parents. This project was approved by the Bioethics Committee of Tehran University of Medical Sciences, Tehran, Iran, by 1396.3068.

Sample size calculation

Sample size of the current study was calculated on the basis of the Cochran formula. By considering type 1 error (α) of 5%, estimation accuracy (d) of 0.05 and prevalence of vitamin D deficiency among Iranian toddlers (31%) [38], the minimum sample size for the current study was 322 participants. However, 425 children aged 6 years were evaluated.

Laboratory assessment

To measure laboratory parameters, a non-fasting blood sample (4 cc each) was obtained from each participant by professional pediatric phlebotomists. All serum samples were placed into special tubes and stored at 4–8 °C. Serum level of 25-hydroxy vitamin D (25(OH)D) was measured by electro-chemiluminescence immunoassay (ECLIA) on a Roche Elecsys system (Roche Diagnosis Elecsys) [39]. Vitamin D deficiency was defined as serum 25(OH)D concentrations less than 10 ng/ml [40]. To evaluate zinc status, the serum concentration of zinc was measured by Atomic

Absorption method (device model: Younglin ASS 8020) [41, 42]. Zinc deficiency was defined as serum levels of zinc less than 70 µg/dl [42]. Serum ferritin levels were determined by the electro-chemiluminescence immunoassay (ECLIA) on a Roche Elecsys system (Roche Diagnosis Elecsys) [43]. Iron deficiency was defined as serum levels of ferritin less than 15 µg [44].

Anthropometric measurements

Weight and height were measured by a trained technician. Children were weighed to the nearest 0.1 kg on calibrated scales wearing light clothing, with shoes removed. Standing height was measured to the nearest 0.1 cm using a portable stadiometer. Body mass index (BMI) was calculated by dividing weight (kilograms) by height squared (meters). The World Health Organization (WHO) growth standards were used to calculate BMI-for-age *Z*-scores. According to WHO criteria, wasting was defined as BMI-for-age *Z*-score of < − 1 SD [45].

Assessment of other variables

Parents were asked to fulfill a self-administered questionnaire which contained information on child's age (year), sex (male/female), birth weight (kg), birth interval (continuous), relevant medical history (diarrhea, respiratory infection, fever) and supplement use (including vitamins D, zinc and iron).

Statistical analysis

Participants were categorized based on tertiles of 25(OH)D and zinc concentrations. To assess the distribution of participants in terms of general characteristics across tertiles of 25(OH)D and zinc concentration, the χ^2 test was used. One-way analysis of variance (ANOVA) was used to determine differences in continuous variables across tertiles of 25(OH)D and zinc concentration. To assess the association of serum levels of 25(OH)D and zinc with wasting, binary logistic regression in different models was applied. In the first model, we controlled for gender (male/female). Further adjustments were applied for region (urban/rural), birth interval (continuous), supplement use including vitamins A and iron (yes/no), relevant medical history including diarrhea, respiratory infection, and fever (yes/no) in the second model. We additionally controlled the analysis for birth weight in the final model. The adjusted variables were obtained from the results of previous studies. For instance, child weight at the age of 6 years is considerably affected by birth weight [46]. Shorter terms of breastfeeding are correlated with higher frequencies of birth intervals under 18 months [47]. These are directly associated with wasting and child weight as well as serum levels of zinc. Therefore, it is necessary to adjust these confounding variables to find an independent association between exposure and outcome variables. We considered the first category of 25(OH)D and zinc concentrations as the reference category. To compute the overall trend of odds ratios across categories of these micronutrients, we considered these categories as an ordinal variable. All statistical analyses were done using SPSS software (version 21.0; SPSS Inc, Chicago IL). *P* values were considered significant at < 0.05.

Results

Of 425 pre-school children participated in the current study, 52.9% were females. The prevalence of vitamin D and zinc deficiencies was 18.8% and 12.7%, respectively. In addition, wasting was prevalent among 31.1% of children.

General characteristics of participants across tertiles of vitamin D and zinc levels are presented in Table 1. Compared with children in the lowest tertile of serum 25(OH)D, those in the highest tertile were more likely to be female, rural resident, and had a longer birth interval. No other significant difference was found for demographic variables across categories of serum 25(OH)D concentrations. Compared with those in the highest tertile of zinc concentrations, the average weight was lower among children in the first tertile. There was no significant difference in terms of demographic characteristics across tertiles of serum levels of zinc.

Multivariable-adjusted OR and corresponding 95% CI for wasting across tertiles of vitamin D and zinc levels are shown in Table 2. Children in the second tertile of 25(OH)D concentration were 53% less likely to have wasting compared with those in the first tertile (OR 0.47, 95% CI 0.27–0.81). After controlling for potential confounders including demographic variables, serum levels of ferritin and zinc as well as birth weight, no significant change was observed (OR 0.47, 95% CI 0.27–0.83). Children in the last tertile of serum concentration of zinc had lower odds of wasting (OR 0.57, 95% CI 0.34–0.96) compared with those in the first tertile. When all potential confounders were adjusted, children in the highest tertile of zinc levels had 47% lower odds of wasting compared with those in the highest tertile (OR 0.53, 95% CI 0.31–0.91).

Discussion

In the present study, the estimated prevalence of vitamin D and zinc deficiencies was 18.8 and 12.7, respectively. We also estimated that wasting was prevalent among 31.1% of Iranian children. We also found that pre-school children in the second tertile of serum 25(OH)D were less likely to

Table 1 General characteristics, anthropometric and biochemical variables across tertiles of vitamin D and zinc levels

	Tertiles of vitamin D			P^b	Tertiles of zinc			P^b
	T1	T2	T3		T1	T2	T3	
Gender (female) (%)	38.3	47.2	55.6	**0.01**	48.5	50.7	42.8	0.39
Region (urban) (%)	73.8	63.4	55.6	**0.006**	64.0	61.2	65.9	0.71
Weight (kg)	20.58 ± 4.51	21.36 ± 4.74	20.81 ± 4.09	0.31	20.32 ± 4.04	20.82 ± 4.65	21.66 ± 4.73	**0.04**
Height (cm)	116.94 ± 7.78	116.97 ± 6.51	117.39 ± 5.95	0.82	116.32 ± 6.67	117.49 ± 6.92	117.61 ± 6.79	0.22
Birth weight (kg)	3.73 ± 1.97	4.14 ± 2.35	4.03 ± 2.19	0.25	3.78 ± 1.91	3.95 ± 2.22	4.21 ± 2.42	0.26
Birth interval (week)	78.05 ± 29.95	84.74 ± 22.93	84.66 ± 24.19	**0.04**	80.56 ± 27.33	85.98 ± 22.54	81.58 ± 26.87	0.18
Supplement use (yes) (%)[a]	8.5	4.2	5.6	0.3	6.6	6.7	3.6	0.45
Relevant medical history (yes) (%)	20.6	19.7	24.6	0.55	19.1	18.7	26.8	0.18
Respiratory infection (%)	9.9	7.7	8.5	0.80	7.4	6.7	10.9	0.40
Diarrhea (%)	4.3	1.4	2.8	0.35	1.5	4.5	2.9	0.34
Fever (%)	7.1	10.6	8.5	0.58	6.6	9.7	9.4	0.60
Ferritin (μg/l)	44.88 ± 25.49	41.27 ± 24.76	41.54 ± 25.17	0.40	40.00 ± 20.65	44.92 ± 28.74	42.26 ± 23.40	0.25
Zinc (μg/dl)	92.67 ± 22.13	92.99 ± 17.59	89.78 ± 20.71	0.35				
Vitamin D (ng/ml)					19.16 ± 9.95	18.82 ± 10.73	18.23 ± 9.42	0.73

Data are presented as mean (SD) or percent

Bold values indicates significant *P*-values (<0.05)

[a]Considered as vitamin A and iron supplements

[b]Obtained from ANOVA and χ^2 tests, where appropriate

Table 2 Odds ratio and 95% confidence interval for wasting across tertiles of serum vitamin D and zinc levels

	T1	T2	T3	P-trend
Serum levels of Vitamin D				
Crude	1	**0.47 (0.27–0.81)**	1.09 (0.67–1.78)	0.70
Model 1	1	**0.48 (0.28–0.82)**	1.11 (0.68–1.82)	0.65
Model 2	1	**0.46 (0.26–0.80)**	1.02 (0.61–1.71)	0.86
Model 3	1	**0.48 (0.27–0.84)**	0.92 (0.54–1.57)	0.81
Model 4	1	**0.47 (0.27–0.83)**	0.92 (0.54–1.56)	0.80
Serum levels of zinc				
Crude	1	0.84 (0.50–1.38)	**0.57 (0.34–0.96)**	**0.03**
Model 1	1	0.84 (0.51–1.39)	**0.57 (0.33–0.96)**	**0.03**
Model 2	1	0.81 (0.48–1.36)	**0.56 (0.33–0.97)**	**0.03**
Model 3	1	0.76 (0.45–1.29)	**0.54 (0.31–0.93)**	**0.02**
Model 4	1	0.75 (0.45–1.27)	**0.53 (0.31–0.91)**	**0.02**

Data are presented as odds ratio (95% CI)

Bold values indicates significant *P*-values (<0.05) and odds ratios

Crude: unadjusted

Model 1: adjusted for Gender

Model 2: model 1 further adjusted for region, birth interval, supplement use (vitamin A and iron supplements), relevant medical history (diarrhea, respiratory infection, and fever)

Model 3: model 2 further adjusted for serum level ferritin, vitamin D and zinc, where appropriate

Model 4: model 3 further adjusted for birth weight

have wasting compared with the first tertile. This association remained significant even after controlling for potential confounders. Children in the last tertile of serum levels of zinc had lower odds of wasting compared with those in the first tertile. After controlling for potential confounders including demographic characteristics, birth weight and serum levels of ferritin and vitamin D, the association remained significant. To the best of our knowledge, this is the first population-based study aimed at discerning the association of zinc and vitamin D levels with wasting among Iranian pre-school children.

Wasting is a public health problem highly prevalent among pre-school children [4]. Wasting is considered as a part of acute malnutrition associated with a higher risk of non-communicable diseases and morbidity from infectious diseases in later life [48]. For children with wasting, the risk of death is approximately threefold higher than those with *Z*-score ≥ − 1 [1, 45]. Micronutrient deficiencies also play a role in malnutrition [49]. The association between micronutrient deficiencies and wasting among pre-school children has long been a question for researchers. In this regard, vitamin D and zinc deficiencies were less studied. We found that pre-school children with moderate levels of 25(OH)D were less likely to have wasting than those with low levels of vitamin D. In line with our finding, Jones et al. [30] reported that wasting, measured by weight-to-height and mid-upper arm circumference (MUAC) *Z*-scores, was inversely associated with serum 25(OH)D concentrations. Underweight children aged 6–36 months were two times more likely to have low levels of serum 25(OH)D (< 42.5 nmol/l) compared with normal-weight children [50]. In a large multi-ethnic cohort study on pre-school children, a significant positive association was found between underweight, measured by BMI Z-score, and vitamin D deficiency (< 50 nmol/l) [51]. Vitamin D deficiency was also positively associated with underweight in children under 3 years of age [52]. In contrast, vitamin D levels were increased with increasing levels of wasting and underweight, measured by weight-to-height *Z*-score, but decreased with increasing levels of stunting among children aged 2–5 years [33]. Moreover, no significant difference in vitamin D levels was observed between the malnourished and non-malnourished children [35]. Others failed to find any significant correlation between vitamin D deficiency and underweight, wasting, and stunting [14, 53].

The inverse association of moderate levels of vitamin D, but not high levels, with wasting might be due to the release of vitamin D from fat tissue in children with wasting. Therefore, wasted children might have a high level of 25(OH)D that is due to wasting. This issue can attenuate the true estimate for the association between vitamin D concentrations and odds of wasting among children.

Recent advancements in vitamin D biology revealed an important role of vitamin D in several extraskeletal tissues including skeletal muscle, immune cells, adipocytes, and pancreatic islets [19]. It was suggested that supplementation with vitamin D may improve weight gain and growth in children [54, 55]. Vitamin D has also been reported to protect against acute infections and accelerate the resolution of inflammatory responses [56]. Since systemic inflammation and infection are related to acute malnutrition and mortality in children [57, 58], the anti-inflammatory properties of vitamin D underlie the inverse association of serum levels of vitamin D and wasting we observed. Moreover, vitamin D may promote elevated parathyroid hormone, leading to calcium influx into adipocytes and enhance lipogenesis [59]. Findings from observational studies have shown that the low levels of 25(OH)D are associated with higher a rate of general and abdominal obesity as well as muscle weakness in children and elderly subjects [60–62]. Vitamin D may affect muscle function through vitamin D receptor (VDR), resulting in muscle growth [63]. This induces the synthesis of new proteins affecting muscle cell contractility, proliferation, and differentiation as well as the regulation of calcium transport in the sarcoplasmic reticulum [64, 65].

In this study, we found an inverse relationship between serum levels of zinc and wasting. A recent meta-analysis indicated that zinc supplementation increased specific growth outcomes in infants and early childhood, particularly in subjects after 2-year supplementation [66]. As previously demonstrated [45, 46], serum levels of zinc are influenced by birth weight and interval. For this reason, multiple regression was conducted, although the correlation values decreased, they remained statistically significant. In line with our findings, Motadi et al. [34] reported that serum levels of zinc are positively associated with anthropometric indices such as weight-to-age, weight-to-height, and BMI-to-age *Z*-scores, and is a predictor of wasting. Serum concentrations of zinc were lower in mildly wasted school children compared with those with normal weight [67]. The prevalence of wasting was high among zinc-deficient children aged 3–18 years [68]. In contrast, several studies have been found no significant correlation of zinc status with wasting in children [33]. Discrepant findings in this regard might be explained by different methods used to assess wasting, adjustments for covariates, and different health condition of children participated in these studies.

Several mechanisms have been suggested for the protective effects of zinc on wasting. The role of zinc in the regulation of appetite, gut absorption, protein utilization, and immune system has been proved previously [69–72]. Growth-stimulating effects of zinc might be mediated through participation in the process of cell proliferation [73]. Circulating levels of zinc increase muscle mass and cell growth through enhancing the secretion of insulin-like growth factor-1 (IGF1) and regulating DNA synthesis [73]. Furthermore, anorexia induced by zinc deficiency leads to a lower intake of energy and protein, essential substrates involved in growth [74].

This was a population-based study with a considerable sample size of 425 children. Although the sample size does not seem to be large enough to generalize the findings, it was followed by a multistage cluster sampling procedure covering a wide region of both rural and urban areas and would partially generable to the entire pre-school children of Iran. However, some limitations should be considered for interpreting our results. The cross-sectional design of the study prohibits inferring a causal relationship between serum levels of vitamin D and zinc with wasting. Prospective studies are needed to confirm our findings. Despite adjustments for relevant confounders, further control for other residual confounding variables including dietary intakes, serum levels of other nutrients and socioeconomic factors are needed to reach an independent association.

In conclusion, the estimated prevalence of vitamin D and zinc deficiencies among Iranian pre-school children, aged 5–7 years, was 18.8 and 12.7, respectively. A significant inverse association was found between serum levels of vitamin D and zinc with wasting either before or after controlling for confounders.

What is already known on this subject?

Earlier studies suggested discrepant findings for the association of wasting from malnutrition with deficiencies of zinc and vitamin D. Some studies revealed that deficiencies of zinc and vitamin D increased the odds of wasting, while others reported no significant association. Moreover, most studies in this regard were from western countries and few data are available from the Middle East where the prevalence of wasting is estimated to be high.

What does this study add?

We estimated that 18.8% of Iranian children, aged 5–7 years, had vitamin D deficiency and 12.7% of them were zinc deficient. We also found a significant inverse correlation between serum levels of vitamin D and zinc with wasting either before or after controlling for confounders.

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Compliance with ethical standards

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Conflict of interest Authors declared no personal or financial conflicts of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards, by 1396.3068.

Informed consent Informed consent was obtained from the parents of children included in the study.

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