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Original Article

Low serum zinc and short stature in children

Kadek Wini Mardewi, I Gusti Lanang Sidiartha, Eka Gunawijaya

Abstract

Background Short stature/stunting is common in developing countries, and has been used as an indicator of a nation's general health condition. Short stature increases the risk of metabolic disease, disturbances in cognitive development, infection prevalence, physical as well as functional deficits, and even death. Nutritional factors that frequently cause stunting are low intake of energy, protein, or micronutrients such as iron, vitamin A, and zinc. The role of zinc supplementation in children with short stature has not been well defined. In addition, zinc supplementation should be evaluated in the setting of specific conditions and regions.

Objective To assess the association between low serum zinc level and short stature in children.

Methods This cross-sectional study was done in a primary health care center at Klungkung I, Klungkung District, from August to September 2013. Children with short and normal stature (as reference group) were enrolled and their serum zinc level was measured, Other risk factors were inquired by questionnaire. Association between low serum zinc level (<65 μg/dL) and short stature was analyzed by stepwise multivariable regression analysis; degree of association was presented as odds ratio (OR) and its corresponding confidence interval.

Results The prevalence of low serum zinc level in our subjects was 71%. Low serum zinc level was significantly associated with short stature [adjusted OR 16.1; 95%CI 3.1 to 84.0; (P=0.001)]. In addition, the occurrence of low serum zinc was higher in the short stature group (88.5%) compared to the normal stature group (53.8%). We also found that low calorie intake was associated with short stature [adjusted OR 29.4; 95%CI 2.76 to 314.7; (P=0.001)].

Conclusion Low serum zinc level appears to be associated with short stature. **[Paediatr Indones. 2016;56:171-5.]**.

Keywords*: zinc; short stature; children*

Short stature (stunting) is commonly found in developing countries and has been used as an indicator of the general health condition of a nation. A survey conducted in Indonesia showed that 31.4% of children had short stature.[1] In Bali, the prevalence of children below 5 years of age with short stature was 36.4%.[2] Short stature increases the risk of metabolic diseases such as type II diabetes in adolescence.[3] In addition, short stature increases the prevalence of infectious diseases, physical as well as functional deficits, and causes death in approximately 2.1 million children below 5 years of age worldwide.[4]

Factors affecting malnutrition in toddlers include genetics, hormones, gender, infectious diseases, and chronic diseases.[5-9] Nutritional factors that cause stunting include low intake of energy, protein, and micronutrients such as iron, vitamin A, and zinc.[10,11] Zinc deficiency may lead to anorexia, which has implications for DNA and RNA synthesis for replication and differentiation of chondrocytes and osteoblasts, declining immune system.[12] Gibson *et al.* found a significant difference in serum zinc in boys with short stature compared to those with normal stature.[11] The role of zinc supplementation in children with short

From the Department of Child Health, Udayana University Medical School/Sanglah Hospital, Denpasar, Bali, Indonesia.

Reprint requests to: Kadek Wini Mardewi, MD, Department of Child Health, Udayana University Medical School/Sanglah Hospital, Jalan Pulau Nias, Denpasar, Bali 80114, Indonesia. Telp. +62-361-244038; Fax +62-361-244038; Email: winimardewi@yahoo.co.id.

stature remains unproven, as previous studies have shown both positive and negative effects.[13,14] The data suggest that populations at high risk of short stature may benefit from zinc supplementation, but local conditions should be taken into account.

The goals of this study were to evaluate the relationships between low serum zinc and the risk of short stature. We secondarily also looked at whether low energy (calorie) intake and protein intake are associated with the risk of short stature in a pediatric population.

Methods

This was a cross sectional study on children with short stature and those with normal stature as the reference group. Subjects were patients who visited one of 39 randomly chosen primary health centers in Klungkung I from August until September 2013, and were aged 24-60 months as well as residents of the area. Inclusion criteria for the 'short stature' group were: 1) children aged 24-60 months with short stature and 2) with parents providing informed consent. Exclusion criteria were: 1) children with chronic diseases such as HIV/AIDS, chronic kidney disease, heart disease, diabetes, or cancer, 2) children with endocrine disorders such as hypothyroidism or Cushing's syndrome, 3) children with bone remodeling disorders such as chondrodystrophy, bone dysplasia, genetic syndromes such as Turner's syndrome, Down syndrome, Kallman's syndrome, Marfan's syndrome, or Klinefelter's syndrome, or 4) subjects' body height to age as adult was still within potential genetic range (MPH). The minimum required sample size was estimated to be 26 subjects per group[15] with two-tail α set at 5%, β=20%, estimated proportion of low serum zinc level in short stature group of 85% and in the reference group 50%.[16]

Subjects were included by systematic random sampling. Screening was done in 4 primary health centers in the Klungkung I area, which were randomly chosen as research sites. We measured body height using a microtoise with an accuracy of 0.1 cm. Body proportion was evaluated in several ways: by comparing sitting height with body height, subischial leg length, and by counting upper segment to lower segment. Lower body segment length was taken by measuring from the upper segment of the pubic symphysis until the sole of the foot. The ratio between the upper and lower segments was compared with standard values for age and sex, then categorized as proportional or non-proportional. Paternal and maternal heights were taken by parental reporting. The mid-parental height (MPH) was calculated and plotted on the *2005 WHO Anthro Curve* to predict the child's height at 20 years of age. As such, knowing the potential genetic body height of a child guided our categorization of children as having short stature due to familial factors or due to other factors.

Subjects were categorized as having short (Z score <-2) or normal stature (Z score ≥ -2 to ≤+2), according to the *2005 WHO Growth Curve* chart for age and sex, using the 2005 *WHO Anthro* software. The short stature and reference groups were matched for gender. Parents filled questionnaires with their complete identity, family characteristics, and subjects' food intake data (calorie and protein intake). Subejcts' serum zinc levels were measured. Calorie intake was the description of children's food consumption, including food ingredients, meal frequency, and total food with protein. Calorie intake was considered to be good if it was ≥ 80% of the recommended daily allowance (RDA) or poor if it was <80% of the RDA. Serum zinc was considered to be low if it was <65 μg/dL.

Data analyses were done by first describing the data using T-test or Chi-square as appropriate. Multivariable analysis with logistic regression (backward stepwise method based on LR) was performed on factors with P values <0.25 on univariable analysis. Results were reported as odds ratio (OR) with 95% confidence intervals and significance level of P<0.05. This study was approved by the Ethics Committee of the Research and Development Unit (Litbang), Udayana University Medical School/Sanglah General Hospital.

Results

During the study period, 174 children aged 24-60 months were screened; 33 (19%) children were found to have short stature. Subjects' characteristics in the short stature and normal height groups are shown in **Table 1**.

Table 1. Baseline characteristics of the subjects

Characteristics	Short stature (n=26)	Normal height (n=26)
Male gender, n	14	14
Mean age (SD), months	38.42 (10.9)	42.15 (10.2)
Calorie intake, n		
< 80% RDA	25	11
≥ 80% RDA	1	15
Protein intake, n		
< 80% RDA	12	3
≥ 80% RDA	14	23
Low serum zinc, n	23	14

Table 2. Univariable analysis of the relationships between research variables and short stature

	Short stature group (n=26)	Normal stature group (n=26)	OR	95%CI	P value
Mean age (SD), months	38.42 (10.9)	42.15 (10.2)	-	-	0.96
Calorie intake, n					
<80% RDA	25	11	34.09	3.99 to 291.16	
>80% RDA	1	15			0.001
Protein intake, n					
< 80% RDA	12	3	6.57	1.57 to 27.43	0.006
≥80% RDA	14	23			
Low zinc serum level, n					
Yes	23	14	6.57	1.57 to 27.43	0.006
No	3	12			

The relationships between each risk factor and short stature on univariable analysis are described on **Table 2**. There was no significant difference in age between the short stature and reference (normal height) groups. However, the mean zinc level was significantly higher in the reference group [72.5 (SD 13.4) μg/dL] than in the short stature group [(54.5 (SD 8.53) μg/dL]; (P=0.001). In addition, Chi-square test revealed that children in short stature group had significant low calorie intake (P=0.001), low protein intake (P=0.006), and low serum zinc level (P=0.006).

Factors, which on univariable analysis had a P value of <0.25 (calorie intake, protein intake, and low serum zinc) were further subjected to multivariable analysis (**Table 3**). A significant association was shown between low serum zinc level and short stature [OR 16.1; 95%CI 3.1-84.0; (P=0.001)].

Table 3. Multivariable analysis of relationships between short stature (short stature group) and low calorie intake, low protein intake, and low serum zinc*

Variable	B	P	OR	95%CI
Calorie intake	3.58	0.005	29.49	2.76 to 314.71
Protein intake	1.21	0.227	3.3	0.47 to 23.87
Low serum zinc level	1.89	0.001	16.16	3.11 to 84.04
Constant	-4.10	0.001	0.01	

*logistic regression test

Discussion

We found that low zinc level and calorie intake was associated with short stature. In our study, subjects in each group were matched for gender as gender may be associated with short stature as well as zinc deficiency. Musthaq *et al*. showed a higher prevalence of short stature in males than in females.[5] Previous studies have also had similar results.[3,6,8] Dehghani *et al*. showed no association between serum zinc level and gender, but zinc deficiency was less common in males (8.1%) than in females (7.8%).[16] In contrast, Ibeanu *et al*. observed that total serum zinc was more common in boys (63.3%) than in girls (36.4%).[17] The zinc level in muscle is higher than in fat.[18] As such, males need more zinc than females because their growth rate is higher and their proportion of muscle per kilogram body weight is larger.

In our study, there was no significant difference in age between the short and normal stature groups. A study showed that prevalence of short stature was highest in children aged 1-4 years, then declined at the age of 5 years (32%), followed by an increase in adolescents aged 14 to 15 years.[3] Another study on short stature also found it to be much higher in children below 5 years of age.[8] This phenomenom appears to be due to increased growth velocity at this age span, thereby increasing the demand for nutrients.

This study showed significant differences between the two groups in both calorie and protein intake. Similarly, Ruminigsih found that toddlers with short stature tended to consume much less energy than toddlers with normal stature.[19]

Protein is a macronutrient required for body growth, development, and function. Hormones and enzymes comprise of proteins with specific chemical functions in the physiological processes of the body. We found that significantly fewer short stature subjects had $\geq$80% RDA of protein than those in the normal stature group. Similar results were reported by Rumininngsih and Tresna.[19,20] The relationship between nutritional status and insulin-like growth factor 1 (IGF-1) in humans can be seen by the decreased IGF-1 level in children with malnutrition like kwashiorkor or marasmic.[21]

Zinc is one of the most important micronutrients affecting children's growth. We found that the mean serum zinc level was significantly lower in the short stature group than in the normal stature group (P=0.001). Gibson *et al.* also found a significant difference in serum zinc levels between boys with short stature [9.19 μmol/L (95%CI 8.53 to 9.84)] and boys with normal stature [9.70 μmol/L (95%CI 8.53 to 9.29). However, in girls they found no differences.[11] Dehghani *et al.* showed signifcantly different result that zinc serum level significantly not related to body height nor body weight.[16] In our study, the short stature group had a significantly greater percentage of subjects with low serum zinc levels compared to the normal stature group.

Low serum zinc may result in short stature, through a zinc-deficiency mechanism which causes anorexia. As such, energy intake is decreased, leading to growth disturbance. Zinc plays a role in both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis, which is important for the replication and differentiation of chondrocytes and osteoblasts, transcriptation, and synthesis of somatomedin, osteoklasin, and collagen, as well as growth hormone (GH) secretion and activation of IGF-1 or somatomedin in liver and bones.[12] Physiologically, more zinc is needed in periods of fast growth to support the processes of DNA replication and transcription, as well as endocrine function.[18,22] Zinc deficiency also contributes to weakening of the immune system thereby increasing the frequency of sickness or morbidity. That, in turn, causes energy and zinc needs that may further disturb linear growth.[12] Zinc supplementation has also been suggested to decrease mortality rates due to pneumonia and diarrhea.[23]

In conclusion, low serum zinc concentration is associated with short stature in children. Low energy (calorie) intake is also related with short stature. In the future, a cohort study is needed in order to further assess the effects of zinc deficiency on short stature. A randomized controlled trial should be performed to evaluate the effects of zinc supplementation on children with short stature.

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Conflict of interest

None declared

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