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Original Article

The mTOR and total protein levels of stunted children

Ria Andreinie[1], Ninik Mudjihartini[2], Dian Novita Chandra[3], Rini Sekartini[4]

Abstract

Background Malnutrition is still a major health problem for children, with stunting being one of its manifestations. Human growth is in part controlled by the mammalian target of rapamycin (mTOR) pathway. Studies reviewing mTOR level and growth disorders in children are still limited and no research has described mTOR levels in stunted children in Indonesia.

Objective To assess for a relationship between mTOR and total protein levels in blood plasma in stunted children aged 6-24 months and compare these levels with those in non-stunted children.

Methods This case-control study was conducted in South Sumatra Province, Indonesia. Subjects were children aged 6-24 months. The inclusion criteria for the case group are children who have a length-for-age of <-2SD and the control group are children who have a body length according to age of more than or equal to -2 SD from the WHO growth standard chart. Anthropometric measurements were plotted on the WHO Growth Standards chart, while mTOR and total protein levels were measured using an ELISA method and spectrophotometry, respectively.

Results Of 142 subjects, 71 children were allocated into each case and control group. Child characteristics that were significantly different between the two groups were age (P=0.002), birth length (P=0.012), weight-for-age Z-score (WAZ) (P<0.001), and body mass index (BMI) (P=0.015).

WAZ status with the categories underweight and severely underweight had a higher risk of stunting. The mTOR and total protein levels between the two groups were not significantly different.

Conclusion Further research is needed to explain the mechanism of mTOR signal deviations in children's growth and development, as mTOR and protein levels are not significantly different in stunted and non-stunted children. **[Paediatr Indones. 2025;65:26-36; DOI: https://doi.org/10.14238/pi65.1.2025.26-36**].

Keywords: *birth length; BMI; child's age; mTOR; protein; stunted; WAZ*

Growth is influenced by two main factors, namely, genetic and environmental factors.[1,2] Growth and development in the womb are "plastic," allowing the baby to prepare itself for the environment outside the womb. However, the postnatal nutritional environment may vary from that in the womb.[3]

In general, health problems that children often experience are malnutrition, poor diet, lack of exercise, and abuse.[4] Adequate nutritional intake results in good nutritional status, whereas an imbalance between nutritional intake and needs results in nutritional disorders or malnutrition.[1,5] Malnutrition in childhood is closely related to several acute diseases, stunted growth and mental development, impaired body immunity; it contributes to around 45% of child deaths worldwide.[6]

The most common form of child malnutrition is stunting. Stunting is characterized as a condition

From the Doctoral Program in Biomedical Sciences[1], Department of Biochemistry and Molecular Biology[2], Department of Nutrition[3] and Department of Child Health[4], Faculty of Medicine, Universitas Indonesia/ Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.

Corresponding author: Ninik Mudjihartini. Department of Biochemistry and Molecular Biology, Faculty of Medicine, Universitas Indonesia. Jl. Salemba Raya No.6, Jakarta Pusat 10430, Indonesia. Telp. (021) 3910734/Fax. (021) 3910190. Email: ninikbiokim@gmail.com

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of growth and developmental retardation observed in children as a result of prolonged inadequate nutritional consumption, recurring infectious illnesses, and insufficient psychosocial interactions.[7] Stunting is of concern to the *World Health Organization* (WHO) because it can cause disturbances in immunological, cognitive, and physical development.[8] Stunting is defined as a length-for-age Z-score of <-2SD (LAZ <-2).[9] In 2018, the WHO reported that 21.9% of children under 5 years worldwide experienced stunting, with Asia in second place with a prevalence of 31.9%. Indonesia had a stunting prevalence of 30.5%.[10]

Studies have revealed that the mammalian target of rapamycin (mTOR) pathway is a key regulatory system that governs human growth. The mTOR functions as a pivotal protein kinase that orchestrates various cellular processes, including metabolism, catabolism, immune responses, autophagy, cellular survival, proliferation, and migration, thereby ensuring the preservation of cellular homeostasis. mTOR is responsible for the phosphorylation of numerous essential proteins, such as AKT, protein kinase C, insulin growth factor receptor (IGF-1R), 4E binding protein 1 (4E-BP1), ribosomal protein S6 kinase (S6K), transcription factor EB (TFEB), and sterol-responsive element-binding proteins (SREBPs). The signaling mediated by mTOR is instrumental in the regulation of translation, lipid biosynthesis, nucleotide production, lysosomal biogenesis, nutrient sensing, and the signaling pathways associated with growth factors.[11,12] The mTOR pathway is a significant intracellular signaling cascade that regulates cell growth and proliferation by monitoring cellular energy levels, mitogenic signals, and nutrition availability.[11] Disruption of the mTOR signaling pathway has been associated with various human diseases, including cardiovascular disease, obesity, neurodegenerative diseases, and metabolic disorders.[12]

The mTOR serves as the catalytic element within two distinct signaling assemblages: mTOR complex 1 (mTORC1) and complex 2 (mTORC2), each encompassing mTOR alongside various supplementary constituents. The operational functionality of mTORC1 is subject to modulation by nutritional factors. Upon activation, mTORC1 triggers processes such as protein biosynthesis, lipid generation, enhancement of ATP synthesis, augmentation of mitochondrial DNA levels, and promotion of oxidative metabolic pathways.[13]

Currently, research examining mTOR levels and growth disorders in children is still limited. To date, there has been no study describing mTOR levels in stunted children in Indonesia. The aim of this study was to determine the relationship between mTOR and total protein levels in children with stunting and compare them to those of normal children.

Methods

This case-control study was conducted in South Sumatra Province, Indonesia, from September to December 2022. Participants were children aged 6-24 months. The sample size was calculated using the formula for hypothesis testing of the difference between two proportions. With an assumed stunting proportion of 0.62 and a 1:1 ratio of cases to controls, the minimum sample size was 67 subjects in each group. The sampling technique was multistage random sampling in three regions of the South Sumatra Province, namely, Palembang City, Muara Enim Regency, and Ogan Komering Ulu Regency.

Inclusion criteria were children aged 6-24 months who were registered at the local community health center and had a growth and development registration card (*KMS/KIA Book*). Children with LAZ <-2SD were allocated into the case group and those with LAZ >-2SD were allocated to the control group.[9] Furthermore, individuals who experienced illness on the specified examination day, were on certain medications, and/or had congenital diseases/syndromes that could affect anthropometric measurements were excluded.

Body length was measured in the supine posture. When measured in standing position, the results for children 0-24 months were adjusted by adding 0.7 cm. An infantometer was used to measure body length of children aged less than 2 years, with an accuracy of up to 0.1 cm. Body weight was measured using a digital scale with an accuracy of up to 0.1 kg 14.

Blood specimens (1-2 mL) were taken from the cubital vein using a *25G BD Vacutainer Safety-Lok®* wing needle (*BD*, Franklin Lakes, New Jersey, USA) and collected into *Vaculab EDTA.K3®* collection tubes (*OneMed*, Krian, East Java, Indonesia), usually

in the morning between 9:00 AM and 12:00 PM. Plasma specimens were prepared as follows: whole blood was centrifuged at 3,500 rpm for 10 minutes to separate the plasma. The plasma was then transferred to a 2.0-mL sterile *Bio-Seen Cat.SGB0020* cryogenic tube (*Bio-Seen*, Shandong, China) and stored at -80°C before further examination.

The mTOR levels were evaluated using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (*Indolisa®* ID-EH10522 human serine/threonine-protein kinase mTOR ELISA kit, *Indogen*, Jakarta, Indonesia). The ELISA procedure was performed according to the manufacturer's instructions and guidelines. Optical density (OD) reading was done using a *Varioskan® Flash* microplate reader (*Thermo Fisher Scientific*, Waltham, MA, USA) at a wavelength of 450 nm; mTOR levels were calculated as pg/mL of plasma.

Total protein levels in plasma were measured using the Christian-Warburg method.[15] The light absorption of the plasma was measured using a spectrophotometer at a wavelength of 280 nm. Total protein concentration was calculated as mg/mL of plasma.

The chi-square test was employed to analyze differences between the two groups' attributes. Mann-Whitney U test was used to analyze non-normally distributed data. The correlation between the traits thought to have the most significant impact on the mTOR levels under investigation was evaluated using Spearman's rank test.

Multivariate analysis with logistic regression test was carried out to analyze various factors associated with risk of stunting in the bivariate analysis, using the normal group as a reference. All variables from the bivariate analysis that have a P value less than 0.25 were included in the final multivariate logistic regression model, which calculated odds ratios with 95%CI. All statistical analyses were carried out using *Statistical Package Social Science* (SPSS) version 20.0 (*IBM Corporation*, Armonk, NY, USA), in which P values <0.05 were considered to be statistically significant.

This research was approved by the Health Research Ethics Committee, Faculty of Medicine, University of Indonesia - RSUPN Dr. Cipto Mangunkusumo and permission was obtained from the provincial and district health departments. All participants' mothers consented to participation in this research.

Results

One hundred fifty-one children aged 6-24 months were initially included in this study, 75 in the control group and 76 in the case group. Subjects underwent anthropometric examinations. Data analysis was done using the per-protocol (PP) method, as we included only participants from whom we successfully obtained blood specimens in the final analysis. Thus, 142 subjects, with 71 subjects in each group, were included in the final analysis (**Figure 1**).

The majority of subjects were aged 12-24 months (78.2%) and more than half were boys (55.6%). Between the case and control groups, there were significant differences in age groups (P=0.002), birth length (P=0.012), WAZ status (P<0.001), and BMI status (P=0.015). Multivariate analysis revealed that children aged 12-24 months had 2.8 times the risk of stunting, birth length in stunted categories had 1.9 times the risk, BMI status in overweight categories had 4.9 the times risk, whereas WAZ in the underweight and severely underweight categories had the highest risk, namely, 82.1 times the risk of stunting (**Table 1**).

The differences in plasma mTOR levels and total protein levels between the case (stunted) and control (non-stunted) groups are shown in **Figure 2**. The median value mTOR level was 229.9 (range 50.8-2742.3) pg/mL in the case group and 215.4 (85.8-2145.2) pg/mL in the control group (P=0.509). The median value total protein level was 95.1 (77.3-212.5) mg/mL in the case group and 94.5 (69.2-128.9) mg/mL in the control group (P=0.271).

Age, gender, gestational age, birth weight and length, exclusive breastfeeding, WAZ, and BMI were not significantly correlated with mTOR levels (**Table 2**). Some of the correlations were positive/unidirectional and some were negative/non-unidirectional, but none were statistically significant (P>0.05).

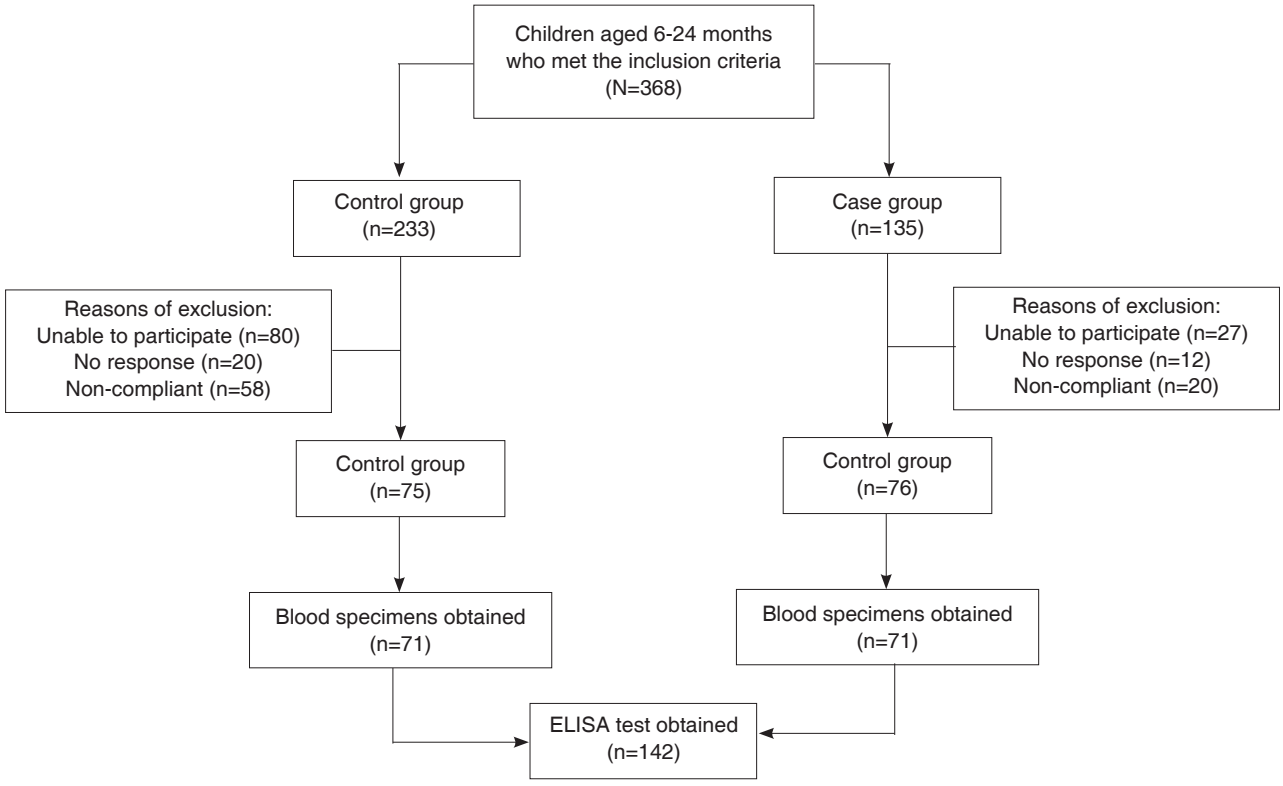


Figure 1. Subject recruitment flow

Discussion

Our results showed that age and stunting were significantly associated, with stunting found in 88.7% of children aged >12 months, yielding a 3.5-fold risk compared to that in children aged <12 months. This finding aligned with that of a study in Ethiopia, which reported that stunting was more common in children aged over 12 months compared to those aged 6-11 months.[16] Similarly, a study of children under 2 years of age in Bangladesh showed that stunting was most prevalent in the older age group, as the rate of stunting in children aged 12 to <24 months was nearly twice as high as in children aged <6 months (OR 2.54; 95%CI 2.21 to 2.92).[17]

Children aged over 12 months are more likely to experience stunting than younger children for several reasons. First, children begin to switch from breast- or formula milk to solid foods at this age. Children over 12 months have more diverse food choices, providing opportunities for unhealthy food consumption, unbalanced nutrition, and low micronutrient content.[18,19] For children aged 1-3 years, the recommended daily intake is as follows: 1,125 kcal of calories, 155 g of carbohydrates, 26 g of protein, 44 g of fat, 16 g of fiber, 1,200 mL of water, 400 mcg of vitamin A, 15 mcg of vitamin D, 6 mg of vitamin E, 15 mcg of vitamin K, 8 mg of iron, 650 mg of calcium, 500 mg of phosphorus, 4 mg of zinc, and 3,000 mg of potassium.[20] Children will only grow to their full potential if their diet meets their nutritional needs; deficiencies in essential nutrients can result from an unbalanced and unvaried diet.[21] In addition, children <12 months tend to experience a decrease in the frequency and duration of breastfeeding. While there are advantages to breastfeeding until two years of age, only a small percentage of children do so. Many children > 12 months begin to wean or cut back on the amount of time they breastfeed.[22] Breastfeeding for >12 months has been associated with higher cognitive abilities and lower rates of non-communicable diseases in adulthood.[23] Third, infection and disease, as children >12 months interact more frequently with their environment. Children living in poor sanitation

Table 1. Characteristics of subjects (N=142)

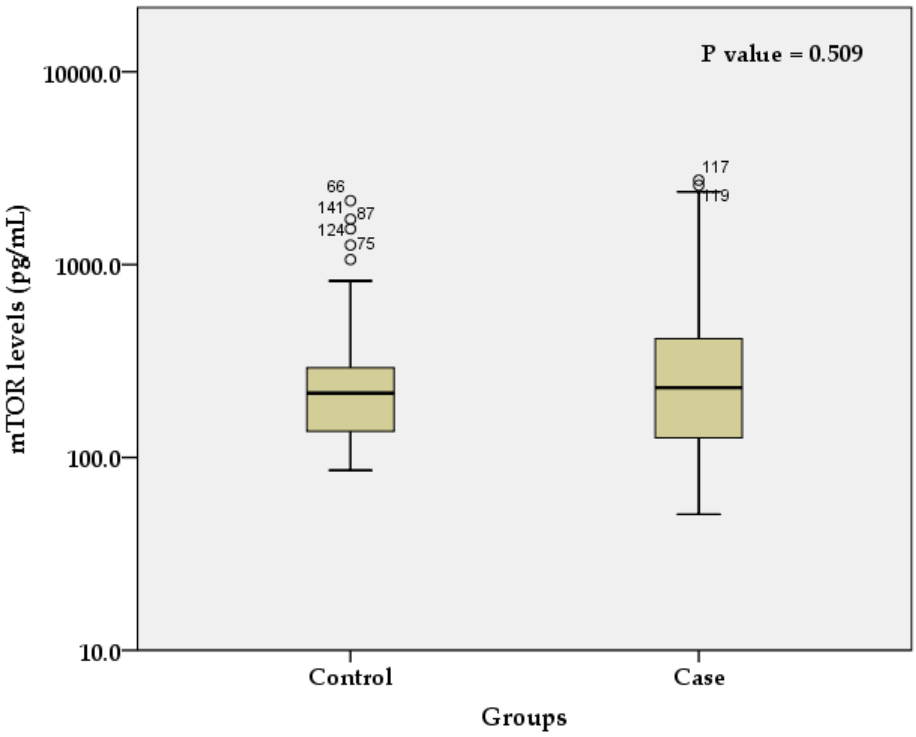
Characteristics	Control (n=71)	Case (n=71)	N=142	P value[a,b]	AOR[c] (95%CI)	P value[c]
Age, n (%)						
6-11 months	23 (74.2)	8 (25.8)	31 (21.8)		1	
12-24 months	48 (43.2)	63 (56.8)	111 (78.2)	0.002[a]*	2.830 (0.843 to 9.496)	0.092
Gender, n (%)						
Female	37 (58.7)	26 (41.3)	63 (44.4)		1	
Male	34 (43.0)	45 (57.0)	79 (55.6)	0.063[a]	1.543 (0.612 to 3.890)	0.358
Gestational age, n (%)						
Full term	60 (51.7)	56 (48.3)	116 (81.7)			
Preterm	10 (43.5)	13 (56.5)	23 (16.2)	0.624[b]		
Post term	1 (33.3)	2 (66.7)	3 (2.1)			
Birth weight, n (%)						
Normal	64 (52.9)	57 (47.1)	121 (85.2)			
Low	6 (33.3)	12 (66.7)	18 (12.7)	0.300[b]		
High	1 (33.3)	2 (66.7)	3 (2.1)			
Birth length, n (%)						
Normal	65 (54.6)	54 (45.4)	119 (83.8)		1	
Stunted	6 (26.1)	17 (73.9)	23 (16.2)	0.012[a]*	1.989 (0.531 to 7.455)	0.308
Exclusive breastfeeding, n (%)						
Yes	48 (49.0)	50 (51.0)	98 (69.0)	0.717[a]		
No	23 (52.3)	21 (47.7)	44 (31.0)			
WAZ status, n (%)						
Normal	63 (74.1)	22 (25.9)	85 (59.9)		1	
Underweight & severely underweight	5 (9.3)	49 (90.7)	54 (38.0)	<0.001[b]*	82.086 (10.479 to 643.028)	<0.001*
Risk of overweight	3 (100.0)	0 (0.0)	3 (2.1)			
BMI status, n (%)						
Normal	60 (55.0)	49 (45.0)	109 (76.8)		1	
Wasted & severely wasted	6 (24.0)	19 (76.0)	25 (17.6)	0.015[b]*	0.187 (0.020 to 1.756)	0.142
Risk of overweight & overweight	5 (62.5)	3 (37.5)	8 (5.6)		4.965 (0.688 to 35.818)	0.112

[a]Chi-square test; [b]Fisher's exact test; [c]logistic regression test, adjusted for age, gender, birth length, WAZ status, and BMI status; *significant; WAZ=weight-for-age Z-score, BMI=body mass index

environments are more susceptible to recurrent infections, such as worms, diarrhea, or respiratory diseases. These infections can reduce appetite and nutrient absorption, increasing the risk of stunting.[24]

Higher stunting rates in older children demonstrate the importance of sustainable interventions since efforts to improve nutrition and water, sanitation, and hygiene behavior are most effective early in improving long-term health outcomes for children. Therefore, the feeding plan for children >12 months calls for giving them a variety of foods from each food group to ensure that they are getting enough nutrients in all forms, giving food in small portions more frequently, emphasizing foods that are high in nutrients, and giving them healthy snacks.[25,26]

In our study, the history of exclusive breastfeeding was not significantly associated with stunting (P=0.717); inconsistent results have been observed in various studies in Indonesia.[27,28] However, optimal breastfeeding for six months reduces the risk of infections that cause stunting. Breast milk contains immunological and anti-inflammatory components, specifically immunoglobulin A (IgA) and immunoglobulin G (IgG), which bind to toxins, bacteria, and viruses and prevent pathogens from attaching to cells. Lactoferrin, a glycoprotein in breast milk that binds iron, also has antimicrobial properties, including the ability to absorb iron, prevent bacterial growth, bind to proteins in bacterial cell membranes, disrupt bacterial integrity, and inhibit pathogen attachment. Together, these compounds transfer specific and non-specific passive immunity from mother to baby, protecting the baby from common pathogens, especially those that cause diarrheal and respiratory diseases.[23]



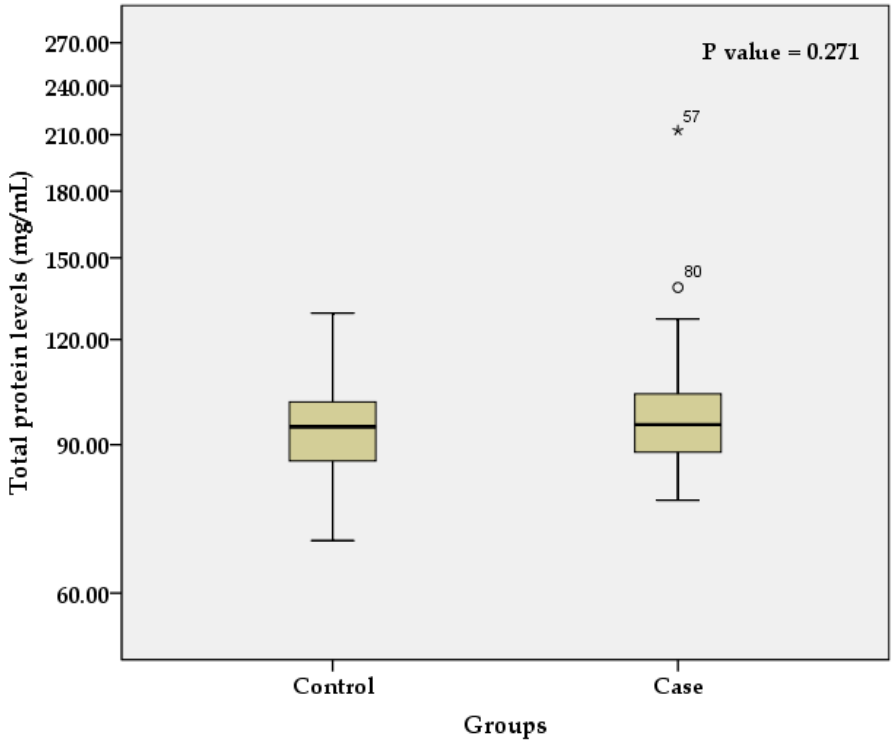


Figure 2. Differences between the case and control groups in: A. mTOR levels and B. total protein levels

Table 2. Analysis of subjects' characteristics and mTOR levels (N=142)

Characteristics	Correlation coefficient	P value[a]
Age	-0.076	0.369
Gender	0.071	0.401
Gestational age	0.132	0.116
Birth weight	-0.020	0.814
Birth length	0.038	0.657
Exclusive breastfeeding	-0.001	0.988
WAZ status	0.083	0.324
BMI status	0.032	0.707

[a]Spearman Rank test

Birth length was significantly associated with stunting (P=0.012), with 2.1 times higher risk in children with stunted birth length. Furthermore, previous studies have shown that stunted children have a history of short birth length.[29,30] Birth length and childhood growth patterns impact the length standard deviation score at 2 years of age, with shorter birth length correlating with growth failure at 24 months in preterm infants.[31] Short birth length can impact a child's height through various mechanisms. Studies have highlighted genetic factors affecting growth, such as by pituitary development, growth hormone (GH)-insulin-like growth factor 1 (IGF-1) or IGF-2 axis variations, and thyroid axis anomalies. Additionally, disturbances in the GH-IGF axis, including lowered IGF-1 levels and increased expression of IGF-binding proteins, can hinder sufficient catch-up growth in children born small for gestational age (SGA).[32] Furthermore, children born SGA may face an increased risk of type 2 diabetes mellitus due to growth retardation in utero, potentially leading to insulin resistance later in life.[33] Metabolic profiles of SGA children without catch-up growth have alterations in cell turnover, GH and IGF-I signaling, and metabolic pathways, shedding light on the molecular mechanisms influencing postnatal growth.[34] These factors collectively contribute to the complex interplay between birth length, genetic influences, and growth hormone pathways in determining a child's final height.

WAZ status had a significant relationship with the prevalence of stunting (P<0.001), with children in the underweight and severely underweight categories having a high-risk level (81.76 times). While this finding may seem unusual, it indicates that the stunting that occurred in our subjects was genuinely caused by malnutrition.

BMI status did not significantly affect mTOR levels. Although the OR indicated a higher risk of stunted growth in the overweight category (OR 4.95; 95%CI 0.688 to 35.818; P=0.112). Children's BMI can reportedly influence his height through the growth hormone (GH) mechanism; the consequence of a high BMI is decreased GH secretion. Additionally, a BMI-for-age above the 85th percentile in childhood was associated with reduced growth, potentially affecting linear growth by approximately 1 cm within four years.[35] Genetic factors also play a role, with a genetic correlation between BMI and changes in height during childhood and adolescence, especially evident in early to middle childhood.[36] These findings highlight the complex interactions between BMI and height in children and emphasize the importance of monitoring both aspects for healthy growth and development.

The mTOR is a conserved protein kinase that is part of numerous cellular processes. It is made up of two complexes, mTORC1 and mTORC2. Though only mTORC1 is regulated by nutrition, both react to growth stimuli.[37] Protein synthesis, cell size, and metabolism are among the growth-related processes that mTOR regulates crucially in healthy and pathological situations. Although mTOR's cytoplasmic activity in controlling translation rate is primarily responsible for these functions, mounting evidence points to other roles that this serine/threonine kinase plays inside the nucleus. Because mTOR may affect the expression of genes involved in ribosomal biogenesis and proliferation, its nuclear activities have been linked to the regulation of protein biosynthesis capability.[38] Our study showed

no statistically significant difference in plasma mTOR levels between the control (non-stunted) and case (stunted) groups (P=0.509). The large variability of mTOR levels in the case group, as illustrated in **Figure 2**, may account for the failure of our statistical methods to detect significant differences.

In stunted children, the body may compensate for the nutritional deficit by adaptively activating mTOR, but this may not occur in all individuals. The mTOR mechanism is influenced by various environmental and metabolic factors. The heterogeneous response to stunting conditions may result in the high variability of mTOR data in our stunted subjects. There is significant heterogeneity in mTOR expression and mTOR signaling, both in reduced signal and signal hyperactivation conditions.[39] The regulation of growth hormone secretion involves mTOR signaling. In particular, mTOR inhibition decreases GH and prolactin secretion, while mTOR activation increases GH secretion in pituitary adenoma cells.[40] Malnutrition in children is linked to dysregulation of the mTOR pathway, specifically decreased phosphorylation of mTORC1, and alterations in gene expression, specifically higher expression of the TSC1 gene and lower expression of the LAMTOR2 gene.[41] These findings provide important information about a possible down-modulation in overall mTOR pathway activity in childhood malnutrition.

The normal range for total protein in the blood is between 6 to 8 g/dL (or the equivalent of 60-80 mg/mL).[42] Various factors, including nutritional intake, the condition of the liver and kidneys, and other health problems, can influence blood protein levels. In our study, total protein in plasma was similar between the case and control groups (P=0.271). The median total protein levels in both groups were above the normal range, namely 95.1 mg/mL and 94.5 mg/mL.

During growth, children need protein to form and repair new body tissue (muscle, skin, and organs), synthesize hormones and enzymes, and form antibodies in the immune system. Protein also plays a role in cellular transport, including the transportation of oxygen, nutrients, and other materials needed to grow body cells.[43] Therefore, it is common to check protein levels in children with suspected nutritional deficiencies. However, we found no significant total protein levels between normal and stunted children. A prospective cohort study also found no correlation between protein intake and linear growth.[44] In addition, another sizable population-based study conducted in the US, a country known for its high protein intake, reported a correlation between higher prenatal protein intake, shorter birth lengths, and slower mid-childhood linear growth, suggesting that higher protein intake may not necessarily positively affect early linear growth.[45] A recent study showed that recombinant SMAD family member 5 (SMAD5) is targeted by miR-24-1-5p, which can reduce the bone mass in children due to a high maternal protein diet.[46] According to this study, eating a lot of protein may deleteriously affect bone mass and osteoblast maturation.

Our study is the first in Indonesia to study the association between mTOR and stunting in children aged 6-24 months. Some limitations of our study include the lack of measurement of other protein complexes directly related to protein synthesis, namely mTORC1 or mTORC2, and lack of assessment of specific protein components that may have provided a better picture of the nutritional status and health of the body, such as albumin and globulin. Another limitation was that we did not exclude subjects who were already receiving nutritional intervention.

In conclusion, WAZ-for-age denoting underweight and severe underweight is an important determining factor in the risk of stunting in children. The focus must be given to providing food that is adequate in quantity and quality starting from the intrauterine period and continuing through postnatal growth. Efforts toward catch-up growth in children with a history growth delays should keep in mind the child's age and illness history to achieve optimal growth. Various cellular mechanisms tightly regulate homeostasis in mTOR levels to maintain proper cellular function, and dysregulation of mTOR signaling can impact energy balance and cause metabolic disorders. Therefore, understanding the signaling dynamics of mTOR and proteins is critical for developing strategies to maintain cellular homeostasis and prevent growth impairment. In the future, more in-depth research will be needed regarding how the mechanism for balancing mTOR and protein levels affects child growth.

Conflict of interest

None declared.

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References

1. Harjatmo TP, Par'i HM, Wiyono S. Penilaian status gizi. Jakarta: Kementerian Kesehatan Republik Indonesia; 2017.
2. Chamidah AN. Deteksi dini gangguan pertumbuhan dan perkembangan anak. J Pendidikan Khusus. 2009;5:83-93.
3. Hildayani R, Sugianto M, Tarigan R, Handayani E, Pudjiati R, Kouri AM. Psikologi perkembangan anak. In: Perkembangan manusia. Jakarta: Universitas Terbuka; 2014.p. 1-34. ISBN 9789790117495.
4. Setiyaningrum E. Buku ajar tumbuh kembang anak usia 0-12 tahun. Sidoarjo: Indomedia Pustaka; 2017.
5. Iqbal M, PDE. Penilaian Status Gizi: ABCD. Jakarta: Salemba Medika; 2018.
6. Ibrahim MK, Zambruni M, Melby CL, Melby PC. Impact of childhood malnutrition on host defense and infection. Clin Microbiol Rev. 2017;30:919-71. DOI: https://doi.org/10.1128/cmr.00119-16
7. WHO. Global nutrition targets 2025: Stunting policy brief. World Health Organization. 2014; [cited 5 Feb 2022]; Available from: http://apps.who.int/iris/bitstream/handle/10665/149019/WHO_N?sequence=1
8. Mayneris-Perxachs J, Swann JR. Metabolic phenotyping of malnutrition during the first 1000 days of life. Eur J Nutr. 2019;58:909-30. DOI: https://doi.org/10.1007/s00394-018-1679-0
9. World Health Organization. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. [cited 5 Feb 2022]. Avalaible from: https://www.who.int/publications/i/item/924154693X
10. World Health Organization. World Health Statistics data visualizations dashboard - child malnutrition - child stunting [cited 5 Feb 2022]. Available from: https://apps.who.int/gho/data/node.sdg.2-2-viz-1?lang=en
11. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. 2017;168:960-76. DOI: https://doi.org/10.1016/j.cell.2017.02.004
12. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell. 2012;149:274-93. DOI: https://doi.org/10.1016/j.cell.2012.03.017
13. Gat-Yablonski G, Luca F De. Effect of nutrition on statural growth. Horm Res Paediatr. 2017;88:46-62. DOI: https://doi.org/10.1159/000456547
14. Kementerian Kesehatan Republik Indonesia. Peraturan Menteri Kesehatan Republik Indonesia Nomor 2 Tahun 2020 tentang Standar Antropometri Anak. 2020 [cited 26 Jul 2023]; Available from: http://peraturan.bpk.go.id/Home/Details/152505/permenkes-no-2-tahun-2020
15. Warburg O, Christian W. Isolierung und kristallisation des garungs ferments enolase. Biochem Z. 1941;310:384-421.
16. Gebreayohanes M, Dessie A. Prevalence of stunting and its associated factors among children 6-59 months of age in pastoralist community, Northeast Ethiopia: a community-based cross-sectional study. PLoS One. 2022;17:e0256722. DOI: https://doi.org/10.1371/journal.pone.0256722
17. Chowdhury TR, Chakrabarty S, Rakib M, Afrin S, Saltmarsh S, Winn S. Factors associated with stunting and wasting in children under 2 years in Bangladesh. Heliyon. 2020;6:e04849. DOI: https://doi.org/10.1016/j.heliyon.2020.e04849
18. Damtie SB, Tefera TB, Haile MT. Dietary diversity practice and associated factors among children aged 6-23 months in Robe Town, Bale Zone, Ethiopia. J Nutr Metab. 2020;2020:919048. DOI: https://doi.org/10.1155/2020/9190458
19. Pries AM, Rehman AM, Filteau S, Sharma N, Upadhyay A, Ferguson EL. Unhealthy snack food and beverage consumption is associated with lower dietary adequacy and length-for-age z-scores among 12-23-month-olds in Kathmandu Valley, Nepal. J Nutr. 2019;149:1843-51. DOI: https://doi.org/10.1093/jn/nxz140
20. Yosephin B. Tuntunan praktis menghitung kebutuhan gizi. Yogyakarta: ANDI Offset; 2018.
21. Harrison M, Brodribb W, Hepworth J. A qualitative systematic review of maternal infant feeding practices in transitioning

from milk feeds to family foods. Matern Child Nutr. 2017;13:e12360. DOI: https://doi.org/10.1111/mcn.12360

22. Chimoriya R, Scott JA, John JR, Bhole S, Hayen A, Kolt GS, *et al*. Determinants of full breastfeeding at 6 months and any breastfeeding at 12 and 24 months among women in Sydney: findings from the HSHK birth cohort study. Int J Environ Res Public Health. 2020;17:5384. DOI: https://doi.org/10.3390/ijerph17155384
23. North K, Gao M, Allen G, Lee ACC. Breastfeeding in a global context: epidemiology, impact, and future directions. Clin Ther. 2022;44:228-44. DOI: https://doi.org/10.1016/j.clinthera.2021.11.017
24. Cameron L, Chase C, Haque S, Joseph G, Pinto R, Wang Q. Childhood stunting and cognitive effects of water and sanitation in Indonesia. Econ Hum Biol. 2021;40:100944. DOI: https://doi.org/10.1016/j.ehb.2020.100944
25. Reidy, KC, Squatrito, C. Programming long-term health: nutrition and diet in toddlers. In: Early Nutrition and Long-Term Health. Woodhead Publishing, 2017. p. 537-60. DOI: https://doi.org/10.1016/B978-0-08-100168-4.00020-3
26. Cowbrough K. Feeding the toddler: 12 months to 3 years - challenges and opportunities. J Fam Health Care. 2010;20:49-52.
27. Paramashanti BA, Benita S. Early introduction of complementary food and childhood stunting were linked among children aged 6-23 months. Jurnal Gizi Klinik Indonesia. 2020;17:1-8. DOI: https://doi.org/10.22146/ijcn.53788
28. Wulandari SD, Lajuna L., Kartinazahri. The relationship between exclusive breastfeeding history and the incidence of stunting in children aged 24-59 months In Kuta Baro District, Aceh Besar Regency. Int J Health Med Res. 2024;03:06. DOI: https://doi.org/10.58806/ijhmr.2024.v3i06n14
29. Elly N, Zainal E, Nilawati I. Maternal factors, gender, and relationship to the length at birth. In: 1st International Conference on Inter-Professional Health Collaboration (ICIHC 2018). Atlantis Press. 2019; p. 328-30. DOI: https://doi.org/10.2991/icihc-18.2019.72
30. Sari K, Sartika RAD. The effect of the physical factors of parents and children on stunting at birth among newborns in Indonesia. J Prev Med Public Health. 2021;54:309-316. DOI: https://doi.org/10.3961%2Fjpmph.21.120
31. Kim S, Choi Y, Lee S, Ahn MB, Kim SH, Cho WK, *et al.* Growth patterns over 2 years after birth according to birth weight and length percentiles in children born preterm. Ann Pediatr Endocrinol Metab. 2020;25:163-8. DOI: https://doi.org/10.6065%2Fapem.1938180.090
32. Toni L, Plachy L, Dusatkova P, Amaratunga SA, Elblova L, Sumnik Z, *et al*. The genetic landscape of children born small for gestational age with persistent short stature. Horm Res Paediatr. 2024;97:40-52. DOI: https://doi.org/10.1159/000530521
33. Renes JS, Van Doorn J, Hokken-Koelega A. Current insights into the role of the growth hormone-insulin-like growth factor system in short children born small for gestational age. Horm Res Paediatr. 2019;92:15-27. DOI: https://doi.org/10.1159/000502739
34. Aoki M, Urakami T, Yoshida K, Nagano N, Morioka I. Three short children born small for gestational age who developed impaired glucose tolerance during growth hormone treatment. Pediatr Int. 2020;62:876-7. DOI: https://doi.org/10.1111/ped.14208
35. Sunder M. Shrinking due to corpulence? BMI in childhood predicts subsequent linear growth among US children and youth, 1963-1970. Ann Hum Biol. 2008;35:432-8. DOI: https://doi.org/10.1080/03014460802232706
36. Silventoinen K, Li W, Jelenkovic A, Sund R, Yokoyama Y, Aaltonen S, *et al.* Changing genetic architecture of body mass index from infancy to early adulthood: an individual based pooled analysis of 25 twin cohorts. Int J Obes. 2022;46:1901-9. DOI: https://doi.org/10.1038/s41366-022-01202-3
37. Jewell JL, Guan K-L. Nutrient signaling to mTOR and cell growth. Trends Biochem Sci. 2013;38:233-42. DOI: https://doi.org/10.1016/j.tibs.2013.01.004
38. Boudra R, Lagrafeuille R, Lours-Calet C, Joussineau CD, Loubeau-Legros G, Chaveroux C, *et al*. mTOR transcriptionally and post-transcriptionally regulates Npm1 gene expression to contribute to enhanced proliferation in cells with Pten inactivation. Cell Cycle. 2016;15:1352-62. DOI: https://doi.org/10.1080/15384101.2016.1166319
39. Winden KD, Ebrahimi-Fakhari D, Sahin M. Abnormal mTOR activation in autism. Annu Rev Neurosci. 2018;41:1-23. DOI: https://doi.org/10.1146/annurev-neuro-080317-061747
40. Xie R, He W-Q, Shen M, Shou X-F, Wang Y-F, Bao W-M, *et al*. Specific inhibition of mTOR pathway induces anti-proliferative effect and decreases the hormone secretion in cultured pituitary adenoma cells. J Neurooncol. 2015;125:79-89. DOI: https://doi.org/10.1007/s11060-015-1895-x
41. Palit P, Gazi MA, Das S, Hasan MM, Noor Z, Ferdous J, *et al*. Exploratory analysis of selected components of the mTOR pathway reveals potentially crucial associations with childhood malnutrition. Nutrients. 2022;14:1612. DOI: https://doi.org/10.3390/nu14081612
42. Pathania AR, Kajal. Chemistry behind serum albumin: a review. In: E3S Web of Conferences. EDP Sciences, 2021. p. 01086. DOI: https://doi.org/10.1051/e3sconf/202130901086

43. Ernawati F, Prihatini M, Yuriestia A. Gambaran konsumsi protein nabati dan hewani pada anak balita stunting dan gizi kurang di Indonesia. Penelitian Gizi dan Makanan. 2016;39:95-102. DOI: https://doi.org/10.22435/pgm.v39i2.6973
44. Berkey CS, Colditz GA, Rockett HRH, Frazier AL, Willett WC. Dairy consumption and female height growth: prospective cohort study. Cancer Epidemiol Biomarkers Prev. 2009;18:1881-7. DOI: https://doi.org/10.1158/1055-9965.EPI-08-1163
45. Switkowski KM, Jacques PF, Must A, Kleinman KP, Gillman MW, Oken E. Maternal protein intake during pregnancy and linear growth in the offspring. Am J Clin Nutr. 2016;104:1128-36. DOI: https://doi.org/10.3945/ajcn.115.128421
46. Ellur G, Sukhdeo SV, Khan MT, Sharan K. Maternal high protein-diet programs impairment of offspring's bone mass through miR-24-1-5p mediated targeting of SMAD5 in osteoblasts. Cell Mol Life Sci. 2021;78:1729-44. DOI: https://doi.org/10.1007/s00018-020-03608-6