Contents lists available at IOCS

Science Midwifery

journal homepage: www.midwifery.iocspublisher.org

Superoxide dismutase (SOD) activity in stunted children: Review article

Leily Badrya[1], Dwirini Retno Gunarti[2], Yohannessa Wulandari[3]

[1,3]Department of of Nutrition, Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

[2]Department of Biochemistry & Molecular Biology, Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

ARTICLEINFO

Article history:
Received Jun 20, 2024
Revised Jun 22, 2024
Accepted Jun 30, 2024

Keywords:
Children,
Deficiency Macronutrients,
Superoxide Dismutase Activity,
Stunting

ABSTRACT

This literature review aims to provide an overview of superoxide dismutase (SOD) activity in stunted children. **Method** is a literature search was done regarding superoxide dismutase activity in stunting. The literature search utilized PubMed to search for published articles, including clinical trials, case reports, and review articles between 2011 and 2023. The result of stunting is a type of chronic malnutrition caused by long-term malnutrition in children. Malnutrition is the cause of 45% of all deaths in children aged <5 years. Deficiency of macronutrients, especially protein and amino acids, especially leucine and arginine in stunting, can cause a decrease in mTORC1 activation, as a pathway in the body's protein synthesis, especially enzymatic synthesis. Disruption of the mTORC1 pathway due to stunting causes a decrease in the synthesis of enzymatic endogenous antioxidants, especially superoxide dismutase (SOD), followed by an increase in free radical molecules in the body. An imbalance between superoxide dismutase (SOD) and an increase in free radicals in stunted children can create short-term impacts, such as recurrent acute infections. There can also be long-term impacts, namely non-communicable diseases, such as obesity, heart disease, and diabetes mellitus in the future. **Conclusion:** based on this literature review, it can be concluded that there is a decrease in the synthesis and activity of superoxide dismutase (SOD) found in stunted children.

Corresponding Author:

Leily Badrya,
Department of Nutrition
Faculty of Medicine, Universitas Indonesia–Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
Email: leily.badrya@gmail.com

INTRODUCTION

In 2022, stunting currently becomes a world concern with the prevalence of stunted toddlers globally from WHO data, by 22,3% with the highest prevalence of stunting being in Asia (World Health Organization (WHO), 2018). Indonesia now ranks fifth globally (Kementerian Kesehatan RI, 2022). The SDGs (Sustainable Development Goals) program targets reducing the incidence of

stunting to be 40% in the world in 2025 (Kementerian Kesehatan RI, 2021). The results of the Indonesian Nutrition Status Survey (SSGI) stated that the prevalence of stunting in children under 5 years of age in Indonesia was 21,6% in 2022, a decrease from 2021 by 24,4% (Kementerian Kesehatan RI, 2022). The target for reducing the stunting rate in Indonesia is 14% by 2024 with an annual reduction reaching 3 to 3,8% (Kementerian Kesehatan RI, 2022; Lalu, 2021).

Stunting is a chronic disorder of the growth and development of children under five and has the potential to cause irreparable negative impacts if not treated immediately. According to WHO, stunting can be caused by chronic malnutrition, such as lack of nutritional intake or increased nutritional needs for a long time, recurrent infections, as well as lack of psychosocial stimulation, especially in the first 1000 days of life. This can lead to impairments, such as difficulty in achieving optimal physical and cognitive development, increased mortality and risk of non-communicable diseases in the future (World Health Organization (WHO), 2018; Soliman et al., 2021). Stunting can be characterized by height/length-for-age z score (HAZ) < -2 SD on the WHO chart caused by chronic malnutrition (World Health Organization (WHO), 2018). Moreover, nutritional problems can be caused by macronutrient and micronutrient deficiencies (World Health Organization (WHO), 2018). Fikawati's study shows that chronic protein deficiency in children causes stunted growth. This study has been conducted in 39 countries, indicating that children who do not consume protein have a 1,4 times greater risk of suffering from stunting (Fikawati et al., 2021).

Antioxidant biomarkers, such as superoxide dismutase (SOD) and pro-oxidants provide a synergistic effect in maintaining the balance of oxidative stress in the body. SOD is the most important and largest endogenous enzymatic antioxidant marker. This plays an important role as the first line function in preventing free radicals in the body. Superoxide is a free radical. Enzymatic antioxidants, such as the SOD enzyme catalyze the change of superoxide into hydrogen peroxide and oxygen (Sychlowy, 1981).

Essential amino acids, especially leucine, and non-essential amino acids of arginine, will specifically bind to their sensors, namely CASTOR1 and sestrin. These can activate mTORC1, causing increased protein synthesis and subsequently increasing the formation of SOD in the body (Li & Yan, 2019; Wolfson & Sabatini, 2017). In addition, arginine specifically stimulates the secretion of Growth Hormone (GH) can increase IGF-1 (insulin-like growth factor-1) (Umeda et al., 2015). Deficiency of protein intake that occurs in stunting, especially deficiency of the amino acids' arginine and leucine, can cause decreased activation of the mTORC1 pathway and decreased SOD synthesis and activity (Munoz & Castilla-Cortazar, 2012).

In the research of Aly, et al., it is said that there is a decrease in levels of the antioxidant superoxide dismutase in stunted children compared to children who are not stunted. SOD can be utilized as an early marker for the development of chronic disease in stunting (Munoz & Castilla-Cortazar, 2012). The specific objectives of Superoxide Dismutase (SOD) activity levels in stunted children can serve as a biomarker for oxidative stress. Identifying reliable biomarkers is essential for understanding the underlying mechanisms of stunting and for developing targeted interventions. Therefore, this literature review aims to provide an overview of the activity of superoxide dismutase (SOD) in stunted children.

RESEARCH METHOD

The design used in this research is a literature review. The literature review was performed using PubMed Central® to search for published articles, including review articles, systematic review and clinical trials between 2011 and 2023. By using Operator Boolean "AND" and "OR", the search keywords used as follows "Superoxide Dismutase", "Antioxidants", "Enzymatic Antioxidant (Endogenous)", "Reactive Oxygen Species (ROS)", "Stunting", "mTORC1", "Leucine", "Arginine", "Insulin-like Growth Factor-1 (IGF-1)", "Protein Synthesis". The total number of articles obtained was 1.350. Of all the articles obtained, the selected literature sources were reviewed and analyzed

by selecting literature that was relevant to the topic of this literature review. The relevant articles used were 34 references.

RESULTS AND DISCUSSIONS

Stunting

Based on the stunting prevalence threshold issued by WHO-UNICEF in 2018, the prevalence of stunting in children under five years is considered high and becomes a public health problem if the prevalence reaches more than 20%. Therefore, the problem of stunting in Indonesia is still relatively high and there is an urgency to accelerate the decline up to 3,5% (Lalu, 2021).

Stunting is a form of chronic malnutrition caused by malnutrition in children and is defined as low/body length compared to chronic nutrition (HAZ) below -2 Standard Deviation (SD) on the 2006 (Arsenault & Brown, 2017; Kementerian Kesehatan Republik Indonesia, 2023). Stunting Standard Curve begins with a retardation in linear growth (linear growth faltering). Retardation of linear growth is defined as a failure to achieve potential linear growth or it can be said that children experience slower growth from children his age (Leroy, et al., 2014).

Malnutrition is a cause of 45% of all children aged <5 years. Stunting broadly inhibits the potential for development and human resources in the country's economy in the future. Children with stunting have a higher risk of morbidity and mortality (Andrew J. Prendegast & Jean H. Humphrey, 2014). Analysis in 53,767 children in Africa, Asia, and Latin America shows that mortality in children with stunting and underweight is obtained three times greater than children with good nutrition (HR 3.4, CI 2.6-4.3) (McDonald et al., 2013).

Pathophysiology of Stunting

Epidemiological studies show that non-optimal breastfeeding, recurrent infections, as well as macronutrients and micronutrients are important proximal determinants of stunting. Although many factors can affect stunting, but the pathogenesis that underlies the failure of linear growth is still not understood (Andrew J. Prendegast & Jean H. Humphrey, 2014; Kementerian Perencanaan dan Pembangunan Nasional Badan Perencanaan dan Pembangunan, 2018).

Complex interactions between mother's nutritional status, endocrine metabolic signals, and placental development regulate fetal growth. Therefore, the size of a newborn reflects the intrauterine environment. The prevalence of low birth weight (<2500 grams) is about six times higher in developing countries compared to developed countries. Mother's malnutrition contributes to around 20% of maternal deaths and increases the risk of child mortality and stunting. Various human and animal studies show that the mother's diet can be a mediation of epigenetic changes in the fetus. Body (Khulan et al., 2012). In a study conducted by Prendergast, et al., there is an increase in inflammatory levels, such as AGP and CRP in stunting groups compared to non -stunted groups (Prendergast et al., 2014). This shows a potential mechanism associated with postnatal growth failure (Andrew J. Prendegast & Jean H. Humphrey, 2014; Prendergast et al., 2014). Children aged 6 to 24 months are one of the critical periods for linear education. Companion feeding refers to the practice of infant and child feeding, such as an introduction to on time food that is safe and nutritious than breast milk. Systematic Review Studies conducted by Dewey, K and Adu explained that there is a best increase in linear growth of +0.7 in HAZ (height-for-age z score) with companion food interventions (Kathryn & Seth, 2008). In addition, there are theories that play a role in pathogenesis stunting, namely the role of the potential pathway mTORC1 associated with the availability of amino acids in children.

The Potential Role of the mTORC1 Pathway in Stunting Pathogenesis

The signal used by the body to control body weight and food intake is considered very complex and involves many paths and has a central control in the hypothalamus, especially in the medial area and peripheral cellular control through mechanistic target of rapamycin complex 1 (mTORC1). The response of the hypothalamic and mTOR system to macronutrients and

micronutrient nutrients is understood associated with nutritional status, psychosocial pressure, endocrine system and linear growth (Semba et al., 2016). The mTORC1 controls the growth and metabolism of all cells in the human body, including bones, skeletal muscles, central nervous system, the digestive tract, blood cells, and other organs that are relevant to stunting in children and morbidity.

Cellular Mechanism of Activation of the mTORC1 Pathway for Protein Synthesis and Linear Growth

The mTOR is a Serin/Threonine Kinase protein that forms the core subunits of two different functional protein complexes, namely mTORC1 and mTORC2. The Mechanistic Pathway (Mechanistic Target of Rapamycin) mTOR has coordination between environmental and intracellular factors to control growth in the body, especially the activation of the mTORC1 pathway, which is much associated with metabolic regulation, translation, autophagy, and growth. Rapamycin mechanistic targets respond to intra and extracellular signals. The mTORC1 has three core components namely mTOR, Raptor (Regulatory Protein associated with mTOR), and MLST8 (Mammalian Lethal with Sec13 Protein 8) (Kim & Lee, 2019). The mTORC1 has the main function of controlling cell growth, while mTORC1 participates in survival control and cell proliferation. mTORC1 regulation responds to the availability of amino acids working on cytosol and lysosomes. These are the main points of mTORC1 signal regulation. About 60 acid hydrolases, lysosomes degrade macromolecules so that the constituent material can be used again in cells (Condon & Sabatini, 2019).

Amino Acid Sensor on the mTORC1 Pathway

The mTOR has stimulation of intra-lysosome amino acids. Amino acids in lysosomes regulate Rag-GTPases through V-ATPase. Mammalia lysosomes have amino acid transports on their surface and are involved in protein degradation, especially as parts of the autophagy process and can also function as a storage of amino acid through a direct binding sensor mechanism with a substrate at physiologically relevant concentrations. Sensor-substrate interactions are needed for their function in the mTORC1 Pathway (Li & Yan, 2019).

Sensors for mTORC1 mediated arginine

Arginine can significantly regulate the signaling of mTORC1 and arginine deficiency suppresses activation in various types of cells. The arginine sensor that has been found for the mTORC1 pathway is CASTOR1 and SLC38A9 (Li & Yan, 2019). Arginine Cytosol Sensors for mTORC1 protein is CASTOR1. If there is sufficient arginine in the body, CASTOR1 binds to arginine causing release to GATOR2, which will inhibit GATOR1 and mTORC1 activation. Conversely, if the condition of the body lacks arginine, CASTOR protein will bind to GASTOR1 so that it will inhibit GASTOR2 (Kementerian Kesehatan RI, 2021). If GATOR2 is inhibited, then GATOR1 is free and causes a negative response to mTORC1 with mTORC1 inactivation. Another sensor related to lysosome arginine (intra -lysosome) is SLC38A9, which is a homologous transmembrane lysosomal protein against amino acid transporter, as a positive regulator for the mTORC1 pathway (Li & Yan, 2019; Wolfson & Sabatini, 2017).

Sensors for mTORC1 mediated by leucine

Leucine is an essential amino acid that functions not only as a constituent of protein synthesis but also signal molecules that regulate protein metabolism including autophagy and mTORC1 pathway. Leucine regulates the mTORC1 pathway through leucine sensors, such as sestrin2 and LARS (Leucyl-tRNA synthetase). LARS is dependent on leucine for mTORC1 activation. This provides a leucine signal to mTORC1 by coupling directly to lysine and then regulates the interaction of RagA and GATOR1, encouraging the formation of RagA containing GTP that has a high GTPase activity. Sestrin has been proven to play an important role in the oxidative damage and mTOR's signal. Sestrin is a group of three Homologous (Sestrin 1-3), which

has long been known as a negative regulator of the mTORC1. Sestrin2 negatively regulates mTORC1 by depending on the GATOR and Rag-GTPases. Sestrin2 binds to GATOR2 freely to the body's condition leucine deficiency and causes mTORC1 inactivation. Leucine stimulation causes a binding to leucine and dissociates from GATOR2, it will free GATOR2 to eliminate GATOR1 regulator inhibitors so that it will activate mTORC1. In cellular stress conditions or chronic deficiency of amino acids, levels of sestrin2 will increase and encourage an increase sestrin2 that binds to GATOR2 and can inhibit the activation of mTORC1. According to this statement, it was found that the mTORC1 pathway was sensitive to the level of leucine and sestrin2 (Li & Yan, 2019; Wolfson & Sabatini, 2017).

IGF1 Activation of the mTORC1 Pathway

Besides the amino acid sensor, insulin-like growth factor-1 (IGF-1) also plays a role in the mTORC1 pathway. IGF-1 will stimulate PI3K signals and activate Akt1. Active Akt1 then do the phosphorylation of TSC, two which causes release from lysosomes and its substrates Rheb. Akt1 directly phosphorylate PRAS40 causes dissociation from the complex, thereby eliminating inhibition and activating mTORC1. PRAS40 is one component of mTORC1 that regulates mTORC1 negatively if Akt is not active (Condon & Sabatini, 2019).

Amino acids leucine, arginine and IGF-1, induce stimulation of protein synthesis by activating the translation process (from mRNA to protein). This process is stimulated by molecular complexes containing Eukaryotic Initiation factors 4E (EIF4E), which are important factors for translation initiation. In a fairly leucine condition in the body, leucine will activate mTORC1. After activated, the mTORC1 will phosphorylate the 4EBP substrate (EIF4E Binding Protein) causing EIF4E dissociation. Furthermore, S6K1 will be active and protein synthesis occurs for growth (Li & Yan, 2019). In the body's condition lacking leucine, then 4EBP will bind to eEIF4E to reduce the activity of the translation initiation complex and suppress translation so that mTORC1 inactivation occurs and does not occur protein synthesis for growth (Kamei et al., 2020). The mTORC1 is very sensitive to the availability of amino acids in the body. Low-quality protein diet patterns are related to stunting, which can cause essential amino acid circulation significantly more than children who are not stunted. The intake of amino acids that can less affect linear growth through the mTORC1 mechanism become the main growth path regulation (Semba et al., 2016).

The Role of mTORC1 Related to Stunting

The role of mTORC1 is related to stunting in children and related morbidity, such as anemia, cognitive disorders, environmental enteric dysfunction, and immunity to infectious diseases. The illustration of the mTORC1 complex role is explained in Figure 1 (Semba et al., 2016; Soliman et al., 2021).

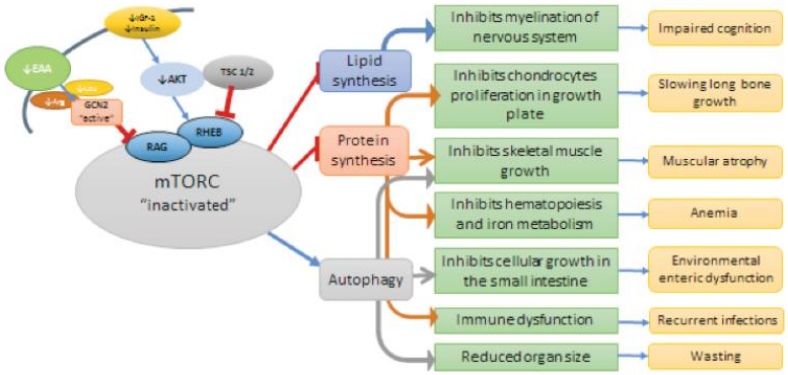

Figure 1. The role of the mTORC complex in stunting pathogenesis

The mTORC1 will suppress protein and lipid synthesis as well as the growth of cells and organisms when the body experiences amino acid deficiency. If the concentration of amino acids is low, then mTORC1 is distributed diffuse in the cytosol and becomes inactive. Besides suppressing protein and lipid synthesis, mTORC1 can also activate autophagy from cells. Autophagy is an adaptation to the hunger of nutrients, the process in which proteins are damaged or excessive and other cells will be sent to the lysosomes and then degraded, releasing free amino acids into the cytoplasm. Protein provides amino acid reservoirs that are mobilized through autophagy when the body is lacking amino acids. In addition, in the absence of other signal amino acids, such as growth and energy factors, these cannot improve the deficiency of amino acids for mTORC1 activation (Soliman et al., 2021).

Oxidative and Antioxidant Stress

Oxidative stress can be interpreted as an imbalance of ROS (Reactive Oxygen Species) and antioxidants in the body. These are part of the redox reaction that receives electrons from other molecules, while the contributor of electrons is called reductant or reducing molecule. ROS is included in oxidants. Then, oxidants and antioxidants have opposite reactions, so in other words, antioxidants are reducing molecules (Sies, 2020).

In physiological conditions, ROS is useful for cells. The low level of intracellular and extracellular ROS (e.g., superoxide and H_2O_2) is very necessary in many biochemical processes, including intracellular signaling, defense against microorganisms, and cell function (Juan et al., 2021; T. & M., 2011). ROS also plays an important role in normal physiological regulation, controlling growth, proliferation, survival, differentiation, and regeneration. ROS production, which is stimulated by nutrition or Growth Factor (GH) functions as a proliferative signal to regulate cell growth and metabolism. For example, hydrogen peroxide oxidizes and deactivates the tyrosine phosphatase protein so that it inhibits its negative role in growth signal transduction (Tsang & Zheng, 2018). However, in some circumstances in a person with protein malnutrition, there is oxidative stress showing the harmful effects for important cellular structures, such as protein, lipids, and nucleic acids. A large amount of evidence shows that oxidative stress is responsible in the beginning or development of several non-communicable diseases, such as diabetes, obesity, cancer, atherosclerosis, and cardiovascular disease (Rahal et al., 2014; Syed et al., 2018).

Antioxidants are compounds that can neutralize free radicals. These are needed by the body to prevent damage caused by free radicals against normal cells in the body. Antioxidant compounds have a molecular structure that can provide electrons to free radical molecules without interfering with function and can break the free radical reaction. Based on the theory of free radicals related to oxidative stress, antioxidants are the first choice to overcome oxidative stress (Rahal et al., 2014). According to their type, antioxidants are divided into enzymatic antioxidants and small molecules, whereas according to the original antioxidant is divided into endogenous and exogenous. Endogenous antioxidants are antioxidant molecules that are naturally produced by the body, while exogenous antioxidants originate from outside the body. Some examples of enzymatic endogenous antioxidants, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx). Some examples of exogenous antioxidants are vitamins, A, C, E, and beta carotene (Moussa et al., 2020).

Superoxide Dismutase (SOD)

Superoxide dismutase (SOD) is an enzymatic endogenous antioxidant. SOD is the largest enzymatic antioxidant and as the first line that functions in ward off free radicals in the body. In humans, there are three types of SOD based on the metal of the cofactor including SOD_1 (Cu/Zn-SOD), SOD_2 (Mn-SOD), and SOD_3 (EC-SOD/SOD Extracellular). ROS production basically depends on enzymatic and non -enzymatic reactions. Enzymatic reactions that are able to produce ROS include those involved in the cellular respiration chain, prostaglandin synthesis, phagocytosis,

and cytochrome system P450. Radical superoxide (O_2•) is produced by NADPH Oxidase, Xanthine Oxidase, and Peroxidase. After being formed, Radical Superoxide (O_2•) is involved in several reactions that will later produce hydrogen peroxide, radical hydroxyl (-OH), peroxynitrite ($ONOO^-$) (Rahal et al., 2014).

$$O_2\bullet + 2\,H^+ \rightarrow H_2O_2 + O_2$$

The primary cellular defense against O2• and peroxynitrite is a group of enzymatic agents called oxidoreductases also known as SOD. As its name indicates, superoxide dismutase works by reducing two superoxides (O2-) to hydrogen peroxide and two more stable oxygen molecules (Karmakar A, et al., 2022; Fukai T and Ushio-Fukai M., 2011).

Superoxide Dismutase in Stunted Children

In children with stunting, there are abnormalities in macromolecular metabolism, including protein. Disruption of protein metabolism due to stunting causes the production of enzymatic endogenous antioxidants to be disrupted, followed by an increase in the body's radical molecules. Aly, et al. proved that there was a significant increase in oxidative stress in 50 stunted children compared to non-stunting children (Aly, et al., 2014).

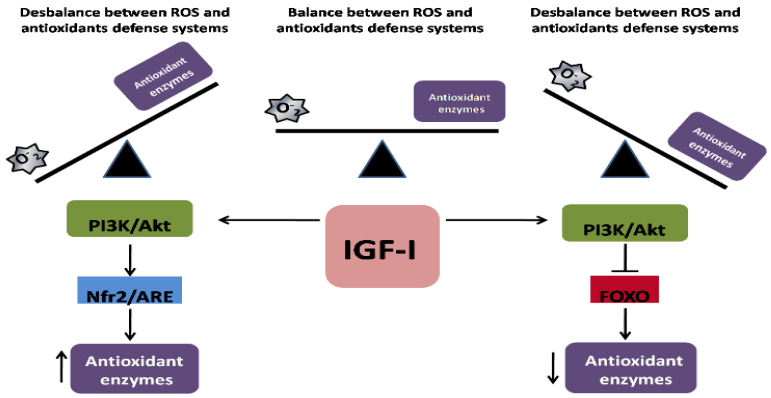

Figure 2. Regulation of enzymatic antioxidants mediated by IGF112

Figure 2 shows the mechanism of IGF1 for enzymatic antioxidants. Insulin plays a cellular role in defense against oxidative stress. IGF1 reduces mitochondrial ROS production via the IGF1/Akt pathway in which Nrf and FOXO are involved. These are transcription factors involved in the expression of enzymatic antioxidants. Nrf under normal conditions is mainly found in the cytoplasm and is responsible for increasing the regulation of various antioxidant enzymes, the expression of anti-inflammatory mediators, as well as increasing enzymes involved in the mitochondrial pathway. When there is exposure to free radicals, Nrf will bind to ARE (Antioxidant Response Element). ARE plays a role in cytoprotection and metabolic enzyme expression. IGF1 can alter the expression of enzymatic antioxidants in opposite ways depending on ROS levels. If there is an increase in ROS, IGF1 will activate the PI3K/Akt pathway then through activation of Nfr2/ARE, it will increase the expression of enzymatic antioxidants, such as superoxide dismutase (SOD). Conversely, if ROS levels are low, IGF1 will reduce the expression of enzymatic antioxidants through inactivation of the FOXO pathway (Munoz & Castilla-Cortazar, 2012).

An imbalance between superoxide dismutase (SOD) and an increase in prooxidants or free radicals in stunted children can cause short-term impacts, namely a decrease in the child's immune system, which can cause children to frequently suffer from acute infections, such as upper respiratory tract infections and digestive infections. Then, there can also be long-term impacts, namely non-communicable diseases, such as obesity, heart disease, and diabetes mellitus in the future (Maggio et al., 2013; Witkowska-Sędek & Pyrżak, 2020).

CONCLUSION

According to this literature review, it can be concluded that there is a decrease found in the synthesis and activity of superoxide dismutase (SOD) experienced by stunted children. The limitation of this research is that not many studies have examined SOD activity in stunted children. Studies examining SOD activity in stunted children are cross-sectional, meaning they provide a snapshot of SOD activity levels at a single point in time. Longitudinal studies are needed to better understand changes in SOD activity over time and their relationship with growth patterns in stunted children. Therefore, further research needs to be carried out to prove a decrease in SOD activity in stunted children and carried out clinical trials to prove the effect of protein or amino acids on SOD activity levels in stunted children.

ACKNOWLEDGEMENTS

The author would like to thank the readers who have reviewed this manuscript. The author declared no potential conflict of interest in this literature review.

References

Aly GS, Shaalan AH, Mattar MK, Ahmed HH, Zaki ME, Abdallah HR. (2014). Oxidative Stress Status in Nutritionally Stunted Children. *Egyptian Pediatric Association Gazette;*62(1):28-33. doi:10.1016/j.epag.2014.02.003

Andrew J. Prendegast, & Jean H. Humphrey. (2014). The Stunting Syndrome in Developing Countries. *Paediatrics and International Child Health*, 250–265

Arsenault, J. E., & Brown, K. H. (2017). Effects of protein or amino-acid supplementation on the physical growth of young children in low-income countries. *Nutrition Reviews*, *75*(9), 699–717. https://doi.org/10.1093/nutrit/nux027

Condon, K. J., & Sabatini, D. M. (2019). Nutrient regulation of mTORC1 at a glance. *Journal of Cell Science*, *132*(21). https://doi.org/10.1242/JCS.222570

Fikawati, S., Syafiq, A., Ririyanti, R. K., & Gemily, S. C. (2021). Energy and protein intakes are associated with stunting among preschool children in Central Jakarta, Indonesia: a case-control study. *Malaysian Journal of Nutrition*, *27*(1), 81–91. https://doi.org/10.31246/MJN-2020-0074

Fukai T and Ushio-Fukai M. (2011). Superoxide dismutases: Role in redox signaling, vascular function, and diseases. *Antioxidants and Redox Signaling*, *15*(6), 1583–1606. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L362292796%0Ahttp://dx.doi.org/10.1089/ars.2011.3999

Juan, C. A., de la Lastra, J. M. P., Plou, F. J., & Pérez-Lebeña, E. (2021). The chemistry of reactive oxygen species (Ros) revisited: Outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. *International Journal of Molecular Sciences*, *22*(9). https://doi.org/10.3390/ijms22094642

Kamei, Y., Hatazawa, Y., Uchitomi, R., Yoshimura, R., & Miura, S. (2020). Regulation of skeletal muscle function by amino acids. *Nutrients*, *12*(1). https://doi.org/10.3390/nu12010261

Karmakar A, Das AK, Ghosh N and Sil PC. (2022). Superoxide dismutase. *In Antioxidants Effects in Health* Jan 1 (pp. 139-166). Elsevier.

Kathryn, G. D., & Seth, A.-A. (2008). Systematic review of the efficacy and effectiveness of complementary feeding interventions in developing countries. *Maternal and Child Nutrition*, *12*(7), 10–17.

Kementerian Kesehatan Republik Indonesia. (2023). *Keputusan Menteri Kesehatan Republik Indonesia Nomor Hk.01.07/Menkes/2147/2023 Tentang Pedoman Nasional Penatalaksanaan Penumonia*.

Kementerian Kesehatan RI. (2021). Buku Saku: Hasil Survei Status Gizi Indonesia (SSGI) 2022. *Kementerian Kesehatan Republik Indonesia*, 1–99. https://promkes.kemkes.go.id/materi-hasil-survei-status-gizi-indonesia-ssgi-2022

Kementerian Kesehatan RI. (2022). Buku Saku: Hasil Survei Status Gizi Indonesia (SSGI) 2022. *Kementerian Kesehatan Republik Indonesia*, 1–99. https://promkes.kemkes.go.id/materi-hasil-survei-status-gizi-indonesia-ssgi-2022

Kementerian Perencanaan dan Pembangunan Nasional Badan Perencanaan dan Pembangunan. (2018).

Pedoman Pelaksanaan Intervensi Penurunan Stunting Terintegrasi di Kabupaten/Kota. *Rencana Aksi Nasional Dalam Rangka Penurunan Stunting: Rembuk Stunting*, *November*, 1–51. https://tnp2k.go.id/filemanager/files/Rakornis 2018/Pedoman Pelaksanaan Intervensi Penurunan Stunting Terintegrasi Di Kabupaten Kota.pdf

Khulan, B., Cooper, W. N., Skinner, B. M., Bauer, J., Owens, S., Prentice, A. M., Belteki, G., Constancia, M., Dunger, D., & Affara, N. A. (2012). Periconceptional maternal micronutrient supplementation is associated with widespread gender related changes in the epigenome: A study of a unique resource in the Gambia. *Human Molecular Genetics*, *21*(9), 2086–2101. https://doi.org/10.1093/hmg/dds026

Kim, J. K., & Lee, J. H. (2019). Mechanistic target of rapamycin pathway in epileptic disorders. *Journal of Korean Neurosurgical Society*, *62*(3), 272–287. https://doi.org/10.3340/jkns.2019.0027

Leroy JL, Habicht JP, González de Cossío T, Ruel MT. (2014). Maternal education mitigates the negative effects of higher income on the double burden of child stunting and maternal overweight in rural Mexico. *Journal of Nutrition*, *144*(5), 765–770. http://jn.nutrition.org/content/144/5/765.full.pdf%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014273286

Lalu, M. (2021). Kebijakan dan Strategi Percepatan Penurunan Stunting di Indonesia. *Bkkbn*.

Li, X. zhi, & Yan, X. hua. (2019). Sensors for the mTORC1 pathway regulated by amino acids. *Journal of Zhejiang University: Science B*, *20*(9), 699–712. https://doi.org/10.1631/jzus.B1900181

Maggio, M., De Vita, F. D., Lauretani, F., Buttò, V., Bondi, G., Cattabiani, C., Nouvenne, A., Meschi, T., Dall'Agli, E., & Ceda, G. P. (2013). IGF-1, the cross road of the nutritional, inflammatory and hormonal pathways to frailty. *Nutrients*, *5*(10), 4184–4205. https://doi.org/10.3390/nu5104184

McDonald, C. M., Olofin, I., Flaxman, S., Fawzi, W. W., Spiegelman, D., Caulfield, L. E., Black, R. E., Ezzati, M., & Danaei, G. (2013). The effect of multiple anthropometric deficits on child mortality: Meta-analysis of individual data in 10 prospective studies from developing countries. *American Journal of Clinical Nutrition*, *97*(4), 896–901. https://doi.org/10.3945/ajcn.112.047639

Moussa, Z., M.A. Judeh, Z., & A. Ahmed, S. (2020). Nonenzymatic Exogenous and Endogenous Antioxidants. *Free Radical Medicine and Biology*. https://doi.org/10.5772/intechopen.87778

Munoz, U., & Castilla-Cortazar, I. (2012). Protection Against Oxidative Stress and "IGF-I Deficiency Conditions." *Antioxidant Enzyme*. https://doi.org/10.5772/51047

Prendergast, A. J., Rukobo, S., Chasekwa, B., Mutasa, K., Ntozini, R., Mbuya, M. N. N., Jones, A., Moulton, L. H., Stoltzfus, R. J., & Humphrey, J. H. (2014). Stunting is characterized by chronic inflammation in zimbabwean infants. *PLoS ONE*, *9*(2). https://doi.org/10.1371/journal.pone.0086928

Rahal, A., Kumar, A., Singh, V., Yadav, B., Tiwari, R., Chakraborty, S., & Dhama, K. (2014). Oxidative stress, prooxidants, and antioxidants: The interplay. *BioMed Research International*, *2014*. https://doi.org/10.1155/2014/761264

RISKESDAS. (2018). Laporan Nasional Riskesdas 2018 Kemenkes RI. *F1000Research*, *10*, 126.

Semba, R. D., Trehan, I., Gonzalez-Freire, M., Kraemer, K., Moaddel, R., Ordiz, M. I., Ferrucci, L., & Manary, M. J. (2016). Perspective: The potential role of essential amino acids and the mechanistic target of rapamycin complex 1 (mTORC1) pathway in the pathogenesis of child stunting. *Advances in Nutrition*, *7*(5), 853–865. https://doi.org/10.3945/an.116.013276

Sies, H. (2020). Oxidative stress: Concept and some practical aspects. *Antioxidants*, *9*(9), 1–6. https://doi.org/10.3390/antiox9090852

Soliman, A., De Sanctis, V., Alaaraj, N., Ahmed, S., Alyafei, F., Hamed, N., & Soliman, N. (2021). Early and long-term consequences of nutritional stunting: From childhood to adulthood. *Acta Biomedica*, *92*(1). https://doi.org/10.23750/abm.v92i1.11346

Sychlowy, A. (1981). Superoxide dismutase. *Materia Medica Polona*, *13*(2), 100–103.

Syed, S., Manji, K. P., McDonald, C. M., Kisenge, R., Aboud, S., Sudfeld, C., Locks, L., Liu, E., Fawzi, W. W., & Duggan, C. P. (2018). Biomarkers of systemic inflammation and growth in early infancy are associated with stunting in young Tanzanian children. *Nutrients*, *10*(9). https://doi.org/10.3390/nu10091158

Tsang, C. K., & Zheng, X. F. S. (2018). A balancing act: mTOR integrates nutrient signals to regulate redox-dependent growth and survival through SOD1. *Molecular and Cellular Oncology*, *5*(5). https://doi.org/10.1080/23723556.2018.1488372

Umeda, M., Hiramoto, M., Watanabe, A., Tsunoda, N., & Imai, T. (2015). Arginine-induced insulin secretion in endoplasmic reticulum. *Biochemical and Biophysical Research Communications*, *466*(4), 717–722. https://doi.org/10.1016/j.bbrc.2015.09.006

UNICEF, WHO, & Group, W. B. (2023). Levels and trends in child malnutrition: Key finding of the 2023

edition. *Asia-Pacific Population Journal*, *24*(2), 51–78.

Witkowska-Sędek, E., & Pyrżak, B. (2020). Chronic inflammation and the growth hormone/insulin-like growth factor-1 axis. *Central European Journal of Immunology*, *45*(4), 469–475. https://doi.org/10.5114/CEJI.2020.103422

Wolfson, R. L., & Sabatini, D. M. (2017). The Dawn of the Age of Amino Acid Sensors for the mTORC1 Pathway. *Cell Metabolism*, *26*(2), 301–309. https://doi.org/10.1016/j.cmet.2017.07.001

World Health Organization (WHO). (2018). Reducing Stunting In Childern: Wquity Considerations for Achieving Global Nutrition Target 2025. *World Health Organization*. https://www.who.int/nutrition/publications/severemalnutrition/reducing-stunting-children-equity/en/