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Immune response in IGF-1 and growth parameters among infected children

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Abstract

Purpose: Infections in children can affect weight gain and linear growth by influencing metabolism and nutrition. Chronic inflammation results in growth failure mediated by pro-inflammatory cytokines and poor nutritional intake, which affects the GH/IGF-1 axis. This study aimed to investigate the impact of the inflammatory response on children's anthropometry, particularly HAZ, and the role of IGF-1. **Methods:** An observational study with a cross-sectional design was conducted from September 2021 to July 2022. The study involved children diagnosed with infections. The subjects had undergone a physical and laboratory investigation, which included a thorax photo, urine culture, Mantoux test, and complete blood test in a hospital setting. A complete medical history was obtained from the pediatrician. **Results:** The prevalence of undernutrition was 37.33%; the prevalence of underweight/severely underweight, stunted/severely stunted, and wasted/severely wasted was 25.33%, 30.66%, and 14.67% respectively. Stunted/severely stunted was more prevalent in subjects under 2 years old, compared to subjects more than 2 years old (22/41 vs. 7/34, p=0.014). SEM analysis revealed that the inflammatory response affected IGF-1 levels (r=0.850, p=0.000), while IGF-1 affected body composition (r=0.245, p=0.025), and then affected HAZ (r=1.000, p=0.000). The effect of IGF-1 on HAZ appears to be indirect, acting through body composition. Parental height has a weak, albeit significant, effect on body composition (r=0.101, p=0.025) and HAZ (r=0.192, p=0.040). Univariate analysis revealed strong correlations between IL-6 and IL-10 and IGF-1 (r=0.870, p=0.000 and 0.876, p=0.000, respectively). In contrast, parental height showed a correlation with HAZ/LAZ (r=0.319, p=0.000). Maternal height was correlated positively with WAZ (r=0.320, p=0.044). **Conclusion:** The prevalence of stunting among children under two years of age indicates that early childhood constitutes a critical period for intervention in growth and development. Inflammatory response has been demonstrated to influence IGF-1 levels in children. The role of IGF-1 on HAZ was mediated by body composition.

Keywords: growth failure; HAZ/LAZ; IGF-1; inflammatory response; undernutrition

INTRODUCTION

Infection in children modulates weight gain and linear growth by influencing metabolism and nutrition [1]. Tuberculosis (TB) in children accounts for 10–20% of all TB cases [2] and is one of the top causes of death globally [3]. Both TB and malnutrition are also bidirectional and increase the risk of mortality [4], even after the implementation of anti-TB drugs [5]. When young children (under five years-old) are infected by Mycobacterium tuberculosis, several immune arrays are blocking its expansion, including macrophage as the first line, neutrophil, dendritic cell (DC) and cell death, and further effects by releasing immune response in the form of inflammatory cytokines (TNF, IL-1, IL-12, and IL-10) [6]. Urinary tract infection (UTI) is a common infection in children [7] and is associated with weight gain [8]. While malnutrition, both underweight or overweight/obesity, was associated with the incidence of UTI (underweight girls OR=1.46 and overweight boys OR=1.41) [8]. This effect on weight gain is due to excessive proinflammatory cytokines (IL-1, IL-6, IL-8) released by the epithelial cells lining the urinary tract, which recruit phagocytes, white blood cells, into the infected area [9].

The relationship between infection and nutrition is bidirectional as frequent illness impairs nutritional status, while poor nutritional status increases infections [10]. Inflammatory status, along with a deterioration of the immune system, was suspected as the cause of inadequate weight gain due to infections, resulting in undernutrition. Undernutrition causes immunocompromisation, so that children are at high risk of dying [11]. Infection occurs with inflammation, which is accompanied by an acute-phase response [12], an innate systemic inflammatory reaction in a host with the consequences of metabolic disruption. Cytokines, released by immune cells as part of the proinflammatory response, induce anorexia, weakness, and fatigue. Metabolically, cytokine production increases the energy and protein requirements to support hepatic acute phase protein (APP) production, such as CRP, and to manifest fever. Moreover, infection also decrease nutrients absorption that cause the micronutrient loss [13], so that infection and inflammation contribute to malnutrition in children [14], perhaps by altering the appetite pathway, particularly in leptin, glucagon-like peptides (GLP-1 and GLP-2) and oxyntomodulin (OXM), also ghrelin secretion that regulated by GH/IGF-1 axis [15]. Other hypotheses suspect that proinflammatory cytokines act as an anabolic function on IGF-1 signalling [16].

Chronic inflammation plays a role in growth failure in children, mediated by proinflammatory cytokines and poor nutritional intake, which affects the GH/IGF-1 axis [17]. IGF-1 is an important growth factor in children, with the highest peak at 6 months of age and the lowest at ~10–11 months of age. Sex affects the levels, with higher levels in girls and an association with children's anthropometry [18]. The mechanism involving this process likely by suppressing GH/IGF-1 axis via several mechanism, including IGF-1 insufficiency or peripheral resistance to GH and/or IGF-1 with further consequences on down-regulation of GH and IGF-1 receptors, disruption in the GH/IGF-1 signalling pathways, dysregulation of IGF binding proteins (IGFBPs), reduced IGF-1 bioavailability, and modified gene regulation [19]. The role of the GH/IGF-1 axis in growth involves the formation of bone and reabsorption, while adipose tissue provides energy for growth requirements. In the adipose tissue, the GH/IGF-1 axis acts to control metabolic function by secreting adipokines [15].

Further findings showed that proinflammatory cytokines also affect the growth plate [17]. Interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) inhibit endochondral ossification via their specific type I cytokine receptors. The high levels of those cytokines suppress growth by decreasing chondrocyte proliferation and hypertrophy while increasing apoptosis. On IGF-1, IL-6 and IL-1β inhibit IGF-1 production in hepatic [20]. The suppression of IGF-1 in chondrocytes occurs in a dose-dependent manner, where IL-6 should be at least 100 ng/ml, by attenuating IGF-1-induced phosphorylation of AKT by 30-50%, and ERK by 50-75%. Those two molecules were the key molecules to stimulate the phosphatidylinositol-3 kinase (PI3K) pathway and the mitogen-activated protein kinase/extracellular signal–regulated kinase (MAPK/ERK) pathway, respectively. By inhibiting those important pathways, cell proliferation was inhibited [16]. The study was conducted to investigate the role of inflammatory response on child anthropometry, particularly HAZ, and the involvement of IGF-1.

METHODS

The study employed an analytic observational cross-sectional design, conducted from September 2021 to July 2022. It involved children diagnosed with infections by a pediatrician in a private hospital (HU, located in Surabaya), utilizing existing medical records from the Outpatient Units. The medical records data, including anthropometric measurements (body weight, head circumference), complete blood tests performed

by the laboratory (including white blood cell count, TNF-α, IGF-1, IL-6, and IL-10), thorax photo, urine culture, etc., were collected from August 2021 to July 2022. We obtained only 75 subjects with complete data, including IGF-1 and pro-inflammatory cytokines.

The subjects underwent physical and laboratory investigations, including thorax photo, urine culture, Mantoux test, and complete blood test, conducted in the hospitals. Complete anamnesis was conducted by the Pediatrician (the researcher). The thorax photo was only interpreted by a radiologist (the same person chosen by the Pediatrician). Inclusion criteria for this study were children aged 12 to 59 months who were brought to visit the Pediatrician in an outpatient facility by their parents.

The subjects must not have chronic disease such as congenital heart disease, genetic malformation (cerebral palsy or Down syndrome), hyperthyroid/ hypothyroid, cow's milk protein allergy, or other immune dysfunction (SLE), or children with malignancy. Exclusion criteria include incomplete medical records. The information on IGF-1, IL-6, and IL-10 measurements was obtained from the data keeper of the Pediatricians. The data also comprises anthropometric data: body weight, body height, weight-for-age z-score (WAZ), height-for-age z-score (HAZ) or length-for-age z-score (LAZ), and weight-for-height z-score (WHZ) or weight-for-length z-score (WLZ) that were determined using WHO Anthro (WHO, offline version). The study has been registered and determined to be ethically appropriate by the Health Ethics Committee of Universitas Airlangga, number 305/EC/KEPK/FKUA/2023.

The data were summarized in descriptive statistics (mean + SD) and frequencies in [n(%)]. Spearman's Rho correlation was used to analyse the univariate correlation. To enrolled structural equation modelling (SEM) we create the latent variables (continuous data): 1) Inflammatory response, consist of IL-6 and IL-10; 2) Parental height, consist of maternal height and paternal height; 3) IGF-1, only consist of IGF-1 levels; 4) Body composition, consist of body weight and body height/length; 5) and HAZ, only consist of HAZ/LAZ. SEM was enrolled using the SmartPLS version. 4.0.

RESULTS

A total of 75 subjects were enrolled in this study. Basic subject characteristics were summarized in Table 1. Age distribution ranged from 12 to 59 months. Table 2 summarizes the categorical data. The study revealed that stunted/severely stunted was more prevalent in subjects under 2 years old, compared to subjects more

Table 1. Subject's characteristics (n=75)

Characteristics	Mean ± SD
Age (months)	25.72 ± 11.10
Maternal height (cm)	156.86 ± 6.07
Gestational age (week)	38.14 ± 2.69
Paternal height (cm)	167.63 ± 6.74
Birth weight (grams)	2,917.80 ± 574.63
Birth length (cm)	48.57 ± 3.07
Mantoux test diameter (cm)	7.79 ± 5.54
Tuberculosis score	5.64 ± 2.30
IL-6 (ng/ml)	128.44 ± 109.92
IL-10 (ng/ml)	461.20 ± 392.12
IGF-1 (ng/ml)	13.59 ± 12.00
Actual body weight (kg)	10.38 ± 2.28
Actual body length/ height (cm)	82.94 ± 9.58
Weight-for-age z-score	-1.44 ± 1.04
Length-for-Age/ Height-for-Age z-score	-1.59 ± 1.09
Weigh-for-length z-score	-0.92 ± 1.02

Table 2. Characteristics of the subjects and nutritional disturbances

Disease characteristics	n	%
Sex		
Male	36	48.00
Female	39	52.00
History of birth		
Normal	43	57.33
Caesarean	32	42.67
Birth weight category		
Term infant	68	90.67
Preterm infant	7	9.33
History of exclusive breastfeeding		
Exclusive breastfeeding	67	89.33
Formula feeding	8	10.67
Formula feeding		
Only breastfed	2	2.67
Breastfed and formula-fed	18	24.00
Formula fed	56	74.67
Type of formula		
Standard follow-on formula	22	29.33
Oral nutritional supplement	45	60.00
Ultra-high temperature (UHT) milk	6	8.00
Breastfed	2	2.67
Medications		
Anti TB	32	42.67
Antibiotics	19	25.33
Anti-TB and antibiotics	24	32.00
Receiving zinc supplementation		
Yes	48	64.00
No	27	36.00
Receiving iron supplementation		
Yes	5	6.67
No	70	93.33
Urine culture		
Positive	46	61.33
Negative	27	36.00
Thorax photo		
Specific lung inflammation	52	69.33
Pleura effusion	5	6.67
Specific lung inflammation and pleural effusion	6	8.00
Bronchitis inflammation	4	5.33
Right suprahilar and pericardial infiltrates	2	2.67
Normal	5	6.67
Bronchopneumonia	1	1.33
Thickening of the right hilum	1	1.33
Suggestive mild bronchopneumonia	1	1.33
Possible specific processes	1	1.33

than 2 years old (22/41 vs. 7/34, p=0.014). Other variables showed no significant difference, including the distribution of undernutrition.

The prevalence of undernutrition was 37.33% (28 of 75 subjects), and according to WAZ, HAZ/LAZ, and WHZ/WLZ categories, the frequencies were summarized in Figure 1. Underweight/severely underweight was 25.33%, stunted/severely stunted was 30.66%, and wasted/severely wasted was 14.67%.

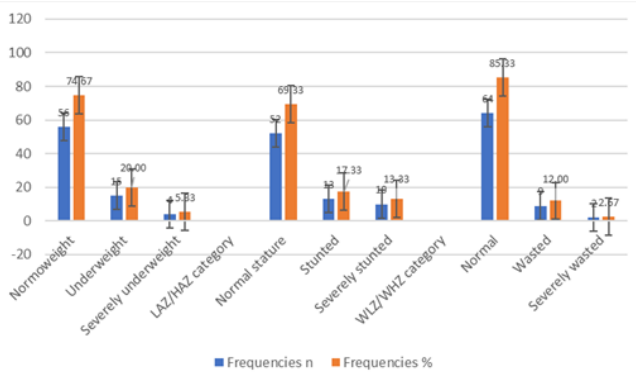

Figure 1. The prevalence of undernutrition is presented as WAZ, LAZ/HAZ, and WLZ/WHZ categories

SEM analysis, summarized in Figure 2, revealed that the inflammatory response affects IGF-1 levels (r=0.850, p=0.000), while IGF-1 affects body composition (r=0.245, p=0.025), and subsequently affects HAZ (r=1.000, p=0.000). The effect of IGF-1 on HAZ appears to be indirect, acting through body composition. Parental height affects body composition (r=0.101, p=0.025) and HAZ (r=0.192, p=0.040) weakly.

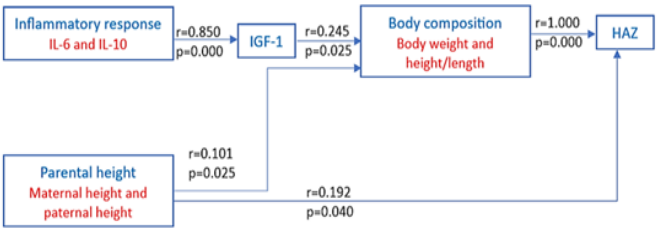

Figure 2. SEM analysis to describe the role of inflammatory response on IGF-1, body composition, and HAZ

Table 3 summarizes the univariate correlation of independent variables (IGF-1, body composition, HAZ/LAZ) on dependent variables (inflammatory response and parental height). Univariate analysis revealed strong correlations between IL-6 and IL-10 and IGF-1 (r=0.870, p=0.000 and r=0.876, p=0.000, respectively). In contrast, parental height showed a correlation with HAZ/LAZ only for paternal height (r=0.319, p=0.000). Maternal height was correlated positively with WAZ (r=0.320, p=0.044).

Table 3. Correlation of immune response (x1) and parental height (x2) on IGF-1 (y1), body composition (y2), and HAZ/LAZ (y3)

Variables	IGF-1		Body weight		Body height		HAZ /LAZ	
	r	p	r	p	r	p	r	p
IL-6	0.870	0.000	0.146	0.213	0.122	0.298	0.110	0.349
IL-10	0.876	0.000	0.104	0.377	0.065	0.578	0.034	0.772
Maternal-height	-0.043	0.791	0.152	0.348	0.083	0.477	0.104	0.373
Paternal-height	0.178	0.273	-0.085	0.600	0.061	0.707	0.319	0.045
IGF-1	-	-	0.131	0.263	0.083	0.477	0.020	0.104

DISCUSSION

The onset of growth faltering was seen in the weaning period until 3 years of life. Children are prone to have nutritional disturbances in the form of stunted and/or underweight and/or wasted [21]. Stunted growth begins with weight faltering, marked by poor weight gain [22]. Acute illness had an adverse effect on the GH/IGF-1 axis via the acute phase response [23]. So, the impact of infections or inflammation on LAZ/HAZ may be indirectly involving IGF-1, or modulating inflammation and metabolic processes [24]. IL-6, as a proinflammatory cytokine, has proven to have an adverse effect on the GH/IGF-1 axis by reducing IGF-1 levels in high levels of IL-6 [23]. Meanwhile, IL-10, as an anti-inflammatory cytokine, may indirectly influence IGF-1 [23] by suppressing the GH/IGF-1 axis, thereby affecting the reduction of IGF-1 and its further impact on growth trajectories [19].

Insulin-like growth factor-1 (IGF-1) is the essential mediator of growth hormone (GH) that is involved in physical growth and metabolic homeostasis [25]. It is crucial for postnatal growth by affecting bone development and height [19]. It plays a role as a key regulator of the action of GH and manages critical processes (cell proliferation, differentiation, and apoptosis). However, the reference value for its normal range has never been established, and no standard measurements have been agreed upon as the gold standard [26]. Due to its importance in mediating GH, IGF-1 was used as an indicator for GH treatment in patients with growth retardation receiving GH therapy. However, IGF-1 levels do not always correlate well with the growth response [27]. IGF-1 acts in a paracrine or autocrine manner, including in bone, as it is produced locally in bone by osteocytes. Not only in the bone, but IGF-1 signalling also occurs in muscle fibers. It acts to stimulate muscle fiber hypertrophy, such as increasing the muscle fiber diameter via protein synthesis and inhibiting protein degradation [28].

IL-6 requires gp130 and IL-6 receptor (IL-6R) for signalling. IL-6R is expressed in osteocytes in high

amounts during gestation. Osteocytes express ADAM 10, which can lead to the release of IL-6R into the serum by breaking the bond between IL-6 and IL-6R. The function of IL-6 is to promote osteoblastic cell differentiation to the mature phenotype. In skeletal muscle, IL-6 was involved in glycogen metabolism and insulin signalling. Moreover, IL-6 induces muscle fiber atrophy [28], which contradicts its role in the muscles.

The contrast finding of IGF-1 and IL-6 explains the muscle weakness in stunted children, as seen in older women with low IGF-1, high IL-6, who had a higher risk of disability (mobility, instrumental activities of daily living) and death [29]. The interaction of IL-6 and IGF-1 results in unfavourable outcomes for human growth, as it increases the proteolytic function of IGF-1-binding protein type 3 (IGFBP-3) and impairs formation of the IGF-I/IGFBP-3/ALS complex. This process results in the shortening of the half-life of IGF-1 and increases IGF-1 clearance. Furthermore, IL-6 excess has a dual effect, increasing osteoclastogenesis and reducing osteoblast activity [30]. Other studies have also noted the unresponsiveness of the liver to GH during systemic inflammation, resulting in decreased IGF-1 levels and a reduction in lean body mass, as demonstrated by in vitro cell culture treated with 10 ng/ml of IL-6 after 24 hours. The effect was fundamentally related to the reduction of STAT5 DNA binding. So, the impact of IL-6 on hepatic GH resistance is time-dependent and dose-dependent [31]. The infusion of IL-6 during intense exercise decreased total IGF-1 level, but increased GH, indicating the modulatory effect of IL-6 on the GH/IGF-1 axis by decreasing IGF-1 in certain conditions [24].

In vitro and in vivo studies have provided undeniable evidence that IGF-1 has immune-modulatory effects. It acts to stimulate the immune system's hypotheses through the augmentation of inflammatory cytokine production in the type 1 T helper cell (Th1) and Th2 by human peripheral blood mononuclear cells (PBMC). IGF-1 stimulation in two ways: stimulating the production of IL-10 by 40-70% in Th2 and stimulating IL-10 mRNA expression by 100-150%. Not only that, but IGF-1 also stimulates IL-4. In contrast with this result, IGF-1 did not stimulate IL-2, IL-5, IL-6, interferon-γ, and the inflammatory cytokines IL-1β, TNF-α [32]. However, an in vitro study in neonatal mononuclear cells (MNC) demonstrated the involvement of IGF-1 in the production of IL-6 and INF-γ by increasing mRNA expression and protein production [16]. This is proven by a positive association of IL-6 and IL-10 with IGF-1 in this study.

The effect of IGF-1 on body measurements (weight and length/height) promotes cell proliferation and differentiation by promoting DNA, RNA, and protein synthesis. Insulin plays specific roles by promoting glucose metabolism and transport. This effect increases the synthesis of fat and glycogen [33].

Regarding anthropometric data, IGF-1 was found to be strongly correlated with age, body height, body weight, and BMI, particularly with body weight (r=0.718) and age (r=0.622), while BMI exhibited a weak correlation (r=0.536) [34]. A positive correlation was observed between infections leading to systemic inflammation and IGF-1 concentration in 18-month-old Malawians, with IGF-1 being positively associated with WLZ, not HAZ [35]. Others noted the correlation with other growth parameters, including LAZ and mid-upper arm circumference. On weight gain, IGF-1 is associated with fat-free mass (FFM), such that every 1.5 ng/mL increment in IGF-1 is followed by a 1-kg increase in FFM [18]. A study examining the correlation of IGF-1 with age, rather than with HAZ or WAZ [26].

This study examined the effect of infections, specifically the release of IL-6 and IL-10, on the body's immune response and IGF-1 levels, but did not include healthy growth-faltering children for comparison. So, we did not have comparable data regarding the effect of immune response on IGF-1 and growth parameters.

CONCLUSION

Stunting is prevalent in children under two years old, suggesting that early childhood is a critical period for growth and development intervention. Inflammatory response influences IGF-1 levels in children. The role of IGF-1 on HAZ was mediated by body composition.

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