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Fecal short-chain fatty acids and growth factors (IGF-1, TGF-β1, Leptin) in stunting children

Ácidos grasos de cadena corta y factores de crecimiento (IGF-1, TGF-β1, leptina) en las heces de niños con retraso del crecimiento

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SUMMARY

Background: *Stunting is not only caused by macronutrient deficiencies but also involves impaired metabolic signaling through the gut-bone axis. Short-Chain Fatty Acids (SCFAs) from the gut microbiota are strongly suspected to influence the secretion of bone growth regulators, including IGF-1, TGF-β1, and leptin. This study aims to analyze the simultaneous effects of SCFA (acetate, propionate, butyrate) on three biomarkers in children with stunting.* **Method**: *A cross-sectional study involving 50 children (25 stunting, 25 non-stunting) aged 36–60 months in West Bandung Regency. SCFA concentrations in feces were measured by gas chromatography, and ELISA analyzed serum biomarkers (IGF-1, TGF-β1, leptin). Data analysis used comparative tests, bivariate correlations, and path analysis.* **Results**: *No significant differences were found in absolute SCFA levels or serum biomarkers between the two groups. However, path analysis showed that in the stunting group, acetic acid exclusively had a strong positive effect on the release of TGF-β1 ($O = 0.751$; $p < 0.001$) and leptin ($O = 0.595$; $p = 0.046$). The effect of SCFA on IGF-1 did not reach statistical significance ($p = 0.143$).* **Conclusion**: *There are changes in metabolic responses in stunting children, in which acetic acid functions as a key signaling molecule that mediates compensatory mechanisms to repair the mucosa (via TGF-β1) and to adapt to malnutrition (via leptin). The failure of the acetate signal to translate into IGF-1 confirms growth hormone resistance due to systemic inflammation (leaky gut).*

Keywords: *IGF-1, Gut-Bone Axis, SCFA, Stunting, TGF-β1*

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RESUMEN

Antecedentes*: El retraso del crecimiento no solo se debe a deficiencias de macronutrientes, sino que también implica una alteración de la señalización metabólica a través del eje intestino-hueso. Se sospecha que los ácidos grasos de cadena corta (AGCC) de la microbiota intestinal influyen en la secreción de reguladores del crecimiento óseo, entre ellos IGF-1, TGF-β1 y leptina. Este estudio tiene como objetivo analizar los efectos simultáneos de los AGCC (acetato, propionato y butirato) sobre tres biomarcadores en niños con retraso del crecimiento.* **Método***: Estudio transversal que incluyó a 50 niños (25 con retraso del crecimiento, 25 sin retraso del crecimiento) de 36 a 60 meses de edad en la Regencia de Bandung Occidental. Las concentraciones de AGCC en las heces se midieron mediante cromatografía de gases y los biomarcadores séricos (IGF-1, TGF-β1, leptina) se analizaron mediante ELISA. El análisis de datos utilizó pruebas comparativas, correlaciones bivariadas y análisis de ruta.* **Resultados***: No se encontraron diferencias significativas en los niveles absolutos de AGCC ni en los biomarcadores séricos entre los dos grupos. Sin embargo, el análisis de trayectorias mostró que, en el grupo con retraso del crecimiento, el ácido acético tuvo un fuerte efecto positivo en la liberación de TGF-β1 ($O = 0,751$; $p < 0,001$) y de leptina ($O = 0,595$; $p = 0,046$). El efecto de los AGCC sobre el IGF-1 no alcanzó significación estadística ($p = 0,143$).* **Conclusión***: Existen cambios en las respuestas metabólicas en niños con retraso del crecimiento, en los que el ácido acético actúa como una molécula de señalización clave que media mecanismos compensatorios para reparar la mucosa (mediante TGF-β1) y para adaptarse a la desnutrición (mediante leptina). La incapacidad de la señal del acetato para traducirse en IGF-1 confirma la resistencia a la hormona del crecimiento debido a la inflamación sistémica (intestino permeable).*

Palabras clave: *IGF-1, Eje intestino-hueso, AGCC, Retraso del crecimiento, TGF-β1*

INTRODUCTION

Stunting is a global nutritional problem with lasting effects on human development. In 2017, about 150 million toddlers worldwide experienced stunting (1). This large number emphasizes the need for a detailed assessment of etiologic factors that extend beyond macronutrient consumption to the molecular and metabolic levels. Stunting has long been linked to inadequate nutritional intake and repeated infections. However, a new perspective suggests that bone health is strongly influenced by the gut microbiota, a concept known as the gut-bone axis. Nutritional intake affects the composition of the microbiota, which in turn plays a crucial role in digestion and absorption. Numerous studies connect the human gut microbiota to health status, including growth, endocrine signaling, and metabolism processes (2,3). Dysbiosis, or an imbalance in the microbiota of stunted children, leads to decreased SCFA, which is thought to be the initial step in disrupting growth signals.

The IGF-1 molecule plays a central role in bone elongation by stimulating the growth plate to expand via increased chondrocyte proliferation and hypertrophy (4,5). SCFAs, especially butyrate, are important natural inhibitors of histone deacetylase (HDAC) enzymes. Normally, HDAC activity deacetylates histones, making chromatin (heterochromatin) more compact and hindering gene transcription. When SCFAs are present, they inhibit HDAC activity, leading to increased histone acetylation (hyperacetylation). This process relaxes chromatin into a more open state called euchromatin, making it easier for genes such as IGF-1 in the liver to be transcribed. In children with stunting and dysbiosis, lower SCFA production may lead to dominant HDAC activity. This can epigenetically suppress IGF-1 gene expression, thereby inhibiting proper growth (6,7).

In addition to acting as signaling molecules, SCFAs—particularly butyrate—serve as the primary energy source for colonocytes and are essential for maintaining gut barrier integrity. In children with stunting, reduced butyrate availability compromises epithelial tight junctions, facilitating the translocation of bacteria and endotoxins such as lipopolysaccharide (LPS) into the bloodstream. This microbial translocation promotes low-grade systemic inflammation. Persistent inflammation is known to induce hepatic resistance to Growth Hormone (GH), thereby impairing IGF-1 synthesis and contributing to growth failure (7,8).

Beyond hormonal pathways, SCFAs also promote bone growth through immune regulation, especially by influencing Transforming Growth Factor Beta-1 (TGF-β1). Both bone and cartilage produce TGF-β1 and are key targets of its

effects. When 9 SCFAs bind to G-protein coupled receptors (GPR43) on immune cells, they activate regulatory T cells (Tregs). These Treg cells are the main producers of the versatile cytokine TGF-β1, which helps decrease systemic inflammation—a common problem in stunting children caused by environmental enteric dysfunction (EED). This decrease creates a more supportive environment for bone formation. Specifically, in bone tissue, TGF-β1 plays a crucial role in starting endochondral ossification, partly by promoting the Wnt-dependent pathway of osteogenesis (9).

Leptin is a hormone predominantly secreted by white adipose tissue, although it is also produced in skeletal muscle, the placenta, and the pituitary gland. As an adipokine, leptin functions as a key regulator of energy availability and metabolic status (10). Short-chain fatty acids (SCFAs), particularly acetate and propionate, activate the G protein–coupled receptors GPR41 (FFAR3) and GPR43 (FFAR2) expressed in adipose tissue. Activation of these receptors stimulates leptin secretion into the circulation. Leptin contributes to bone growth through two complementary mechanisms: it modulates Growth Hormone (GH) secretion via hypothalamic pathways, and it acts directly on growth plate chondrocytes by binding to leptin receptors, thereby promoting chondrocyte proliferation, differentiation, and endochondral bone formation (11-13).

In stunted children, reduced fat mass and gut dysbiosis markedly limit adipose GPR receptor stimulation, primarily due to insufficient SCFA availability. This impaired receptor activation contributes to persistently low leptin levels, which the body interprets as a signal of energy scarcity. Under these conditions, the endocrine system shifts toward conserving energy for essential metabolic functions rather than supporting growth. This adaptive response ultimately exacerbates growth failure (14,15).

IGF-1, TGF-β1, and leptin act synergistically to regulate bone growth. IGF-1 and leptin promote the proliferation and differentiation of bone cells, whereas TGF-β1 stimulates extracellular matrix synthesis and contributes to early proliferative signaling within the growth plate (4,11,16). Although the association between gut dysbiosis and stunting has been widely documented, most studies have focused primarily on alterations in bacterial taxonomic composition or on overall SCFA levels. Consequently, the specific contributions of individual SCFA types to key bone-growth regulators remain poorly understood. This study therefore aimed to simultaneously evaluate the effects of acetate, propionate, and butyrate on three major regulators of bone growth—IGF-1, TGF-β1, and leptin—to elucidate the molecular mechanisms linking the gut–bone axis to stunting pathogenesis.

METHOD

This cross-sectional study included children aged 36–60 months in West Bandung Regency, classified as stunted or non-stunted. Data on the characteristics of both groups were collected during integrated health services (Posyandu).

The sample size was selected using statistical calculations to estimate the mean difference at the 95% confidence level. This study involved 50 children, comprising 25 stunted and 25 non-stunted, selected using consecutive sampling. Stunting criteria were determined based on World Health Organization (WHO) standards: a height-for-age (H/A) z-score $<$ -2 SD, with non-stunting children having a z-score $\geq$ -2 SD. Exclusion criteria included children with low TSH concentrations (<0.90 μIU/mL), undergoing steroid treatment, or having congenital disabilities. Written consent from the parents of these children was obtained before the study's initiation.

Subject characteristics included age, gender, weight, and height, measured during activities at the integrated health post (posyandu). The independent variable was the fecal concentration of SCFAs (acetic acid, propionic acid, and butyric acid), and the dependent variables were the serum concentrations of IGF-1, TGF-β1, and leptin.

Enzyme-Linked Immunosorbent Assay (ELISA)

Circulating concentrations of IGF-1, TGF-β1, and leptin were quantified using a commercial double-sandwich enzyme-linked immunosorbent assay (ELISA) kit from ELK Biotechnology (Wuhan, China). All reagents and 96-well microplates coated with specific capture antibodies were conditioned at room temperature before use. Specifically, for TGF-β1 analysis, serum samples were first acid-activated using 1N HCl and neutralized with 1.2N NaOH/0.5M HEPES to separate the active form of the cytokine from the Latency-Associated Peptide (LAP) bond.

A total of 100 μL of serum sample (diluted with Assay Diluent to fall within the kit's detection range) and the standard solution were added to the appropriate microplate wells. The plate was covered and incubated for 80 minutes at 37°C to facilitate antigen-antibody binding. After discarding the solution (without washing), 100 μL of biotin-conjugated specific detection antibody (Biotin-conjugated Detection Antibody) was added to each well, followed by incubation for 50 minutes at 37°C. The microplate was washed three times with 1X Wash Buffer. Next, 100 μL of the Horseradish Peroxidase (HRP)-Streptavidin conjugate was added to each well to bind the biotinylated antibody, and the wells were incubated in the dark at 37°C for 50 minutes. After five washes, the colorimetric reaction was initiated by adding 90 μL of the tetramethyl-benzidine (TMB) substrate. The plate was incubated again in the dark at 37°C for 20 minutes until a blue color gradient was formed, proportional to the amount of antigen. The enzymatic reaction was precisely stopped by adding 50 μL of a sulfuric acid-based stop solution, which instantly changed the solution's color from blue to yellow. The optical absorbance (OD) of each well was measured immediately at 450 nm using a microplate reader. The actual concentrations of IGF-1, TGF-β1, and leptin in the samples were calculated from the standard calibration curve using 4-parameter logistic regression (4-PL) software.

Gas chromatography-mass spectrometry (GC-MS) method

The fecal SCFA concentrations (acetic acid, propionic acid, and butyric acid) were analyzed by gas chromatography-mass spectrometry (GC-MS). A 100 mg fecal sample was placed in a centrifuge, 0.25 mL of 50% sulfuric acid was added, and the mixture was vortexed for 3 minutes. Next, 1 mL of diethyl ether was added, and the mixture was vortexed again for 3 minutes. The suspension was then centrifuged at 6000 rpm for 5 minutes. The organic phase was removed and transferred to a separate centrifuge tube. After the organic phase was collected and homogenized, the solution was injected into the GC-MS. The GC-MS instrument was first conditioned to its optimum condition. Inject 1 μL of sample at an inlet temperature of 160°C with a split ratio of 1:10 and using helium carrier gas (1.0 mL/min). The oven temperature program started at 80°C (held for 1 min), increased by 15°C/min to 115°C (held for 3 min), then by 3°C/min to 130°C, and finally by 15°C/min to 230°C (held for 3 min). Molecular detection was carried out using the Electron Impact ionization mode (EI, 70 eV) and Selected Ion Monitoring (SIM) to monitor specific ions precisely: m/z 60 (acetic acid), 74 (propionic acid), and 88 (butyric acid and IS). Final quantification was calculated based on the regression of the internal standard calibration curve and expressed in mM.

Statistical Analysis

Data analysis was performed using SPSS version 25 software (IBM Corp.). Descriptive statistics were used to assess baseline characteristics. Independent t-tests and Mann-Whitney tests were used to compare mean differences between groups. Relationships between variables were evaluated using bivariate correlations (Pearson/Spearman), followed by path analysis using structural equation modeling to examine the simultaneous effects of SCFAs on biomarkers. Statistical significance was set at $p < 0.05$.

Ethical Clearance

This research has received ethical approval from the Research Ethics Committee of the Faculty of Medicine, Hasanuddin University, with the recommendation No. 893/UN4.6.4.5.31/ PP36/2024 dated October 22, 2024, and was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Table 1 shows that height (89.71 ± 5.13 cm vs. 98.75 ± 3.86 cm; $p < 0.001$) and weight (11.94 ± 1.38 kg vs. 14.02 ± 1.44 kg; $p < 0.001$) were significantly lower in the stunting group. The mean age of the stunting group (44.64 months) was also younger than that of the non-stunting group ($p = 0.026$). No significant differences were found in birth weight ($p = 0.183$) and birth length ($p = 0.148$), indicating that stunting in these subjects was postnatally acquired faltering.

Measurement of gut microbiota metabolites, as reflected in Short-Chain Fatty Acid (SCFA) profiles in feces, showed no significant differences between the two study groups. Median values for acetic acid concentrations (39.29 and 42.82; $p = 0.923$), propionic acid (20.29 and 22.28; $p = 0.877$), and butyric acid (20.42 and 22.37; $p = 0.318$) were comparable between stunting and non-stunting children. Although the non-stunting group tended to have slightly higher absolute values for these three short-chain fatty acids, the very wide ranges in both groups prevented this difference from reaching statistical significance.

In line with the fecal metabolite findings, evaluation of systemic biochemical parameters in the blood circulation also showed no significant differences. Concentrations of the growth hormone IGF-1 were equivalent between the stunting and non-stunting groups (0.52 and 0.65, respectively; $p = 0.265$). A similar pattern was observed for measurements of the immune-regulating cytokine TGF-β1 (0.07 and 0.06; $p = 0.676$) and the energy metabolism-regulating adipokine leptin (2.18 and 1.79; $p = 0.980$). Overall, these comparative

Table 1. Characteristics, anthropometric measurements

Variable	Stunting Group (n=25)	Non-Stunting Group (n=25)	p-value
	Mean ± SD	Mean ± SD	
Age	44.64 ± 7.93	49.08 ± 5.45	0.026
Birth weight	2904 ± 293.66	3004 ± 371.35	0.183
Birth length	47.92± 2.93	49.12 ± 1.51	0.148
height	89.71 ± 5.13	98.75 ± 3.86	0.0001
weight	11.94 ± 1.38	14.02 ± 1.44	0.0001
	Median (Min-Max)	Median (Min-Max)	
Acetic acid	39.29 (2.04-138.08)	42.82 (5.07-141.48)	0.923
Propionic acid	20.29 (7.29-89.23)	22.28 (4.69-85.19)	0.877
Butyric acid	20.42 (7.03-69.02)	22.37 (1.18-55.76)	0.318
IGF-1	0.52 (0.28-2.44)	0.65 (0.36-1.07)	0.265
TGF-β1	0.07 (0.04-0.14)	0.06 (0.05-0.19)	0.676
Leptin	2.18 (0.56-4.92)	1.79 (0.04 -7.40)	0.980

baseline data indicate that absolute values of metabolic and immunological biomarkers did not differ between groups.

Bivariate correlation analysis was performed to evaluate the relationship between Short-Chain Fatty Acids (SCFA) levels, including acetic acid, propionic acid, and butyric acid, with growth biomarkers (IGF-1), immunomodulators (TGF-β1), and energy metabolism regulators (leptin). Comparison of correlation outcomes between stunting and non-stunting children revealed significantly different patterns of metabolic interactions, as presented in Table 2.

The main findings of this study showed a highly statistically significant positive correlation between the entire SCFA profile and TGF-β1 levels, which occurred only in the stunting children group. Acetic acid showed the strongest positive correlation ($r = 0.796$; $p < 0.001$), followed by butyric acid ($r = 0.618$; $p = 0.001$) and propionic acid ($r = 0.546$; $p = 0.005$). In contrast, in the non-stunting children group, all SCFA variants showed a weak, negative, non-significant correlation. This suggests that increased SCFA production in stunting children is directly related to increased TGF-β1 cytokine secretion.

In contrast to the TGF-β1 profile, analysis of the growth hormone IGF-1 did not find a significant correlation with SCFA levels in either group. In the stunting group, acetic, propionic, and butyric acids showed only very weak positive correlations ($r = 0.155$, 0.152, and 0.271), with p-values that were not significant.

The correlation between SCFAs and leptin levels showed a similar pattern to that of IGF-1. No statistically significant correlation was found between acetic, propionic, and butyric acids and circulating leptin in either the stunting group ($p = 0.161$; $p = 0.239$; $p = 0.180$) or the non-stunting group ($p = 0.243$; $p = 0.203$; $p = 0.196$). In the stunting group, the correlation coefficient was weak and positive ($r < 0.300$), whereas in the non-stunting group it was weak and negative ($r < -0.300$).

Path analysis was used to examine the direct effects in a multivariate way, as shown in Table 3, and Figures 1 and 2. In the stunting group, acetic acid was the only predictor with a positive and statistically significant effect on two parameters. First, acetic acid had a very strong positive effect on increasing TGF-β1 levels ($O = 0.751$; $p < 0.001$). Second, acetic acid also showed a significant positive effect on leptin secretion

Table 2. Relationship between SCFA and growth factors

Biomarkers / SCFAs	Stunting Group		Non-Stunting Group	
	r	p-value	r	p-value
IGF-1				
Acetic acid	0.155	0.46	-0.23	0.269
Propionic acid	0.152	0.469	-0.159	0.264
Butyric acid	0.271	0.19	-0.043	0.838
TGF-β1				
Acetic acid	0.796	0.001*	-0.32	0.119
Propionic acid	0.546	0.005*	-0.377	0.099
Butyric acid	0.618	0.001*	-0.267	0.198
Leptin				
Acetic acid	0.289	0.161	-0.242	0.243
Propionic acid	0.245	0.239	-0.264	0.203
Butyric acid	0.277	0.18	-0.268	0.196

Table 3. Effect of SCFA on Growth Factor

	Stunting Group		Non-Stunting Group	
	Original sample (O)	p-value	Original sample (O)	p-value
IGF-1				
Acetic acid	0.582	0.143	-0.361	0.253
Propionic acid	-0.361	0.467	0.242	0.633
Butyric acid	-0.083	0.862	0.008	0.932
TGF-β1				
Acetic acid	0.751	0.0001*	-0.031	0.932
Propionic acid	-0.359	0.204	-0.115	0.793
Butyric acid	0.388	0.285	-0.305	0.308
Leptin				
Acetic acid	0.595	0.046*	-0.145	0.679
Propionic acid	-0.13	0.803	0.14	0.745
Butyric acid	-0.241	0.687	-0.349	0.174

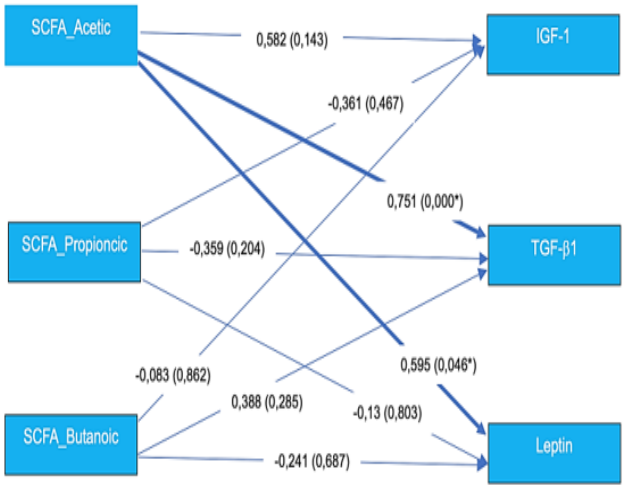

Figure 1. Path Analysis in the stunting group

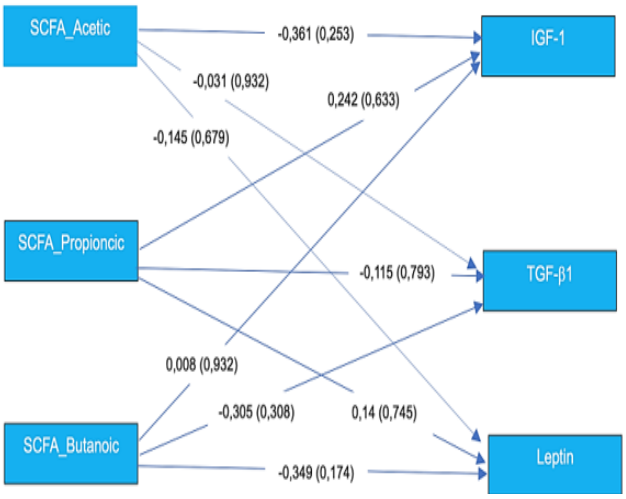

Figure 2. Path analysis in the non-stunting group

(O=0.595; p=0.046). In contrast, propionic acid and butyric acid did not have a significant effect on any parameters in this group (p >0.05).

Regarding IGF-1, no significant effect was observed for any SCFA in the stunting group. Although acetic acid showed a positive path coefficient (O = 0.582), this value was not statistically significant (p = 0.143).

In the non-stunting group, analysis showed no significant effect of any SCFA variant (acetate, propionate, and butyrate) on circulating IGF-1 or TGF-β1. All path coefficients in this group had p-values > 0.05, indicating that fluctuations in fecal SCFA levels during eubiosis (healthy gut) do not directly affect systemic growth factor secretion.

DISCUSSION

This study demonstrates the complex interaction between SCFA production and growth factors in children with stunting, from the perspective of the gut-bone axis. Our data show no significant differences in SCFA levels between the two groups. Interestingly, although total fecal SCFA concentrations were fairly equal between stunting and non-stunting children, there were significant changes in the body's response to these metabolites. These results suggest that stunting is not solely related to decreased SCFA production in the intestinal lumen but also involves disruptions in systemic immunometabolic signaling. In this chronic malnutrition, acetic acid plays a key role in mediating physiological adaptation mechanisms.

These results are particularly interesting, demonstrating equivalence in fecal concentrations of acetic, propionic, and butyric acids between the two study groups.

It is known that the intestines of stunting children have a different microbiota composition (dysbiosis) and are very lacking in bacterial metabolites (17). However, from a clinical-pathophysiological perspective, this same condition provides valuable clues about the disorder's true locus. In stunting toddlers in developing countries, persistent exposure to enteric pathogens during the complementary feeding period often triggers a condition known as Environmental Enteric Dysfunction (EED). EED is characterized by villous atrophy, crypt hyperplasia, and, most importantly, a loss of the protective barrier provided by the intestinal epithelial cell tight-junction protein network, leading to leaky gut syndrome (18).

Under eubiotic conditions, a healthy gut, such as that in the non-stunting group, produces SCFAs, particularly butyrate, which colonocytes use directly as a primary energy source through beta-oxidation. SCFAs improve barrier function by reducing intestinal epithelial permeability and strengthening tight junctions (19). In contrast, in children who experience stunting with EED, acetic acid, the smallest SCFA and the one with the highest concentration in the lumen, is not converted much by colonocytes. Hence, it undergoes massive translocation through the leaky epithelium (leaky gut) into the lamina propria and the bloodstream (20). This is why, even though SCFA levels in the lumen (feces) appear normal, the flow of SCFAs into the bodies of stunting children can be altered, potentially resulting in a signal deficit needed to trigger the IGF-1 growth axis (21).

Through pathway analysis, this study clearly demonstrates a close relationship between all SCFAs and TGF-β1, primarily due to the direct influence of acetic acid. TGF-β1 is a pleiotropic cytokine critical for immune regulation and mucosal tissue repair. The significant effect of acetate on TGF-β1 in the stunting group suggests a defence mechanism that helps the body cope with this condition.

Molecularly, high levels of acetate that penetrate the intestinal lamina propria will be recognized and bind specifically to G-protein coupled receptors, namely FFAR 1 (GPR41) and FFAR2 (GPR43), which are widely expressed on the surface of local immune cells, including macrophages and T-regulatory cells (Treg) (6,2). This ligand-receptor binding functions as a Histone Deacetylase (HDAC) inhibitor that epigenetically changes chromatin, stimulates Treg cell differentiation and secretion of the anti-inflammatory cytokine TGF-β1, and controls the chondrogenesis process (22-24). Therefore, the effect of acetate on TGF-β1 production in stunted children is not pathological but rather a precise compensatory mechanism. The body actively utilizes acetate as a signal to reduce local inflammation and stimulate structural protein synthesis to repair the intestinal mucosa damaged by EED (8,25).

The research results reveal a new finding: acetic acid positively affects leptin secretion, especially in children with stunting. Physiologically, we know that leptin levels are usually proportional to the amount of white adipose tissue (26). Children with stunting typically have very low-fat reserves, leading to low leptin levels. Interestingly, however, the fact that acetate can significantly increase leptin suggests that leptin in stunting acts as an immunomodulator (27).

Systemic acetate can reach adipose tissue and activate FFAR2 receptors on adipocytes (24). In the context of stunting, the interaction between acetate and leptin suggests a broader physiological role for leptin beyond its classical function as a satiety hormone. Under these conditions, leptin acts primarily as an immunomodulatory adipokine (27). During periods of energy scarcity and increased risk of microbial translocation from the gut, acetate stimulates the remaining adipose tissue to release leptin. This leptin response contributes to the regulation of innate immune function and supports the maintenance of basal metabolic rate (28,29). Such adaptations indicate that, in stunted children, the endocrine system prioritizes energy allocation toward immune defense rather than anabolic growth, thereby reinforcing growth impairment.

Growth hormone (GH) resistance and suppression of the IGF-1 axis are central components of the gut–bone axis hypothesis. This model proposes that SCFAs can enhance hepatic IGF-1 production, thereby promoting longitudinal bone growth by stimulating the epiphyseal growth plate (30). In the present study, the pathway coefficient linking acetic acid to IGF-1 in stunted children was positive and of considerable magnitude, yet it did not reach statistical significance. This pattern suggests that, despite the presence of an upstream acetate signal, the downstream hepatic response is blunted. Such a disconnect is consistent with the classical pathophysiology of stunting, in which chronic inflammation contributes to hepatic GH resistance, ultimately impairing IGF-1 synthesis.

Although acetate-derived signals from the intestine may attempt to stimulate hepatic IGF-1 gene transcription, stunting occurs within a systemic pro-inflammatory cytokine environment—characterized by elevated IL-6 and TNF-α—originating from increased intestinal permeability. This low-grade inflammation is known to inhibit the JAK2/STAT5b signaling pathway in hepatocytes, thereby reducing the liver's responsiveness to both GH and SCFA-mediated stimulation. As a result, IGF-1 synthesis becomes suboptimal despite the presence of upstream metabolic cues (11,31). These findings underscore a critical implication: nutritional interventions aimed at promoting linear growth are unlikely to be fully effective unless the gut environment and its associated inflammatory processes are clinically addressed.

In a state of eubiosis, intestinal and systemic homeostasis are maintained. Consistent with this, our analysis showed that none of the SCFA variants had a significant effect on IGF-1, TGF-β1, or leptin levels in the non-stunted group. This finding is biologically plausible: in adequately nourished children with an intact intestinal mucosa, immunometabolic balance has already been achieved. The production of TGF-β1 and energy-regulating hormones such as leptin follows physiological circadian patterns and endocrine feedback loops, independent of fluctuations in SCFA concentrations. Under these conditions, SCFAs primarily support routine digestive and metabolic functions rather than activating compensatory signaling pathways in bone or adipose tissue.

While this study introduces a novel mechanism regarding the role of acetic acid in stunting, several limitations should be acknowledged. First, the cross-sectional design restricts causal inference and prevents assessment of temporal relationships. Additionally, we were unable to directly measure systemic inflammatory markers such as IL-6 or CRP, or specific indicators of intestinal permeability such as fecal zonulin. These biomarkers would have strengthened the interpretation of our findings, particularly regarding the contribution of microbial translocation and hepatic GH resistance to impaired IGF-1 synthesis.

CONCLUSION

This study demonstrates that the role of short-chain fatty acids (SCFAs) extends beyond serving as an energy substrate for colonocytes to functioning as systemic signaling molecules that support metabolic adaptation during chronic malnutrition. Our findings suggest that, in

stunted children, acetic acid acts as a central mediator of the adaptive response associated with Environmental Enteric Dysfunction (EED). The selective increase in TGF-β1 and leptin secretion in response to acetate indicates a compensatory mechanism in which the body prioritizes mucosal repair and innate immune support over anabolic growth. Furthermore, the inability of acetate to effectively stimulate the IGF-1 axis is consistent with hepatic hormone resistance driven by persistent low-grade systemic inflammation.

These observations have important clinical implications: nutritional interventions aimed at promoting linear growth in stunted toddlers are unlikely to achieve optimal outcomes unless intestinal inflammation is concurrently addressed. Future strategies for stunting management should therefore emphasize restoration of gut barrier integrity and targeted nutritional approaches that modulate the SCFA ecosystem and its downstream signaling pathways.

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Conflicts of Interest

All authors declare that there is no conflict of interest in this research.

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