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ASSOCIATION BETWEEN THE SOMATOTROPIC AXIS AND ENDOTHELIAL NITRIC OXIDE SYNTHASE IN CHILDREN WITH COVID-19 AND MULTISYSTEM INFLAMMATORY SYNDROME

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Abstract.

The influence of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) on endothelial nitric oxide synthase (eNOS) represents a key mechanism in maintaining vascular homeostasis and cardiovascular functional status. Endothelial dysfunction may coincide with somatotropic axis disturbances in children with COVID-19, particularly those with multisystem inflammatory syndrome (MIS-C), yet these interactions remain poorly characterized.

***The aim of this study** is to determine the association between GH and IGF-1 levels and eNOS concentrations in children with COVID-19 and MIS-C.*

***Materials and methods.** Ninety children aged 1 month to 17 years were enrolled: 63 with COVID-19, 15 with MIS-C, and 12 controls without evidence of SARS-CoV-2 infection. GH, IGF-1, and eNOS concentrations were quantified using enzyme-linked immunosorbent assay kits: hGH AccuBind ELISA Kit (Cat. No. 1725-300; Monobind Inc., USA), Human IGF-1 (Insulin-like Growth Factor 1) ELISA Kit (Cat. No. E-EL-H0086; Elabscience, USA), and Human NOS3/eNOS (Nitric Oxide Synthase 3, Endothelial) ELISA Kit (Cat. No. E-EL-H0755E-EL-H0755; Elabscience, USA). Approved by the Bioethics Committee of I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine (Protocol No. 71, October 25, 2022), the study was conducted following ethical standards. Statistical analysis, performed using IBM SPSS Statistics and GraphPad Prism software, considered differences statistically significant at $p < 0.05$. This research formed part of the project «Clinical phenotypes and pathogenetic mechanisms of COVID-19 and multisystem inflammatory syndrome in children, and risk stratification of post-COVID disorders in children with comorbid pathology» (state registration No. 0126U000023; 2026-2028).*

***Results.** Decreased GH and IGF-1 levels correlated with lower eNOS values, as evidenced by significant positive correlations between these parameters ($p < 0.05$): $r_{GH\text{-}eNOS}=0.27$; $r_{IGF\text{-}1\text{-}eNOS}=0.21$. Children infected with SARS-CoV-2 exhibiting low IGF-1 levels demonstrated significantly lower eNOS values relative to those with normal IGF-1 levels ($p = 0.008$): 411.70 (300.90; 499.80) ng/mL versus 478.80 (413.60; 622.70) ng/mL, respectively. Multiple linear regression analysis of eNOS predictors revealed that the GH-inclusive model failed to reach statistical significance (adjusted $R^2 = 0.022$; $p = 0.250$), despite GH showing a weak independent positive association with eNOS levels ($\beta = 0.23$; $B = 30.55$; $p = 0.048$); by contrast, the IGF-1-inclusive model indicated that increased IGF-1 concentration was associated with higher eNOS levels ($\beta = 0.50$; $B = 1.94$; $p < 0.001$) and achieved statistical significance (adjusted $R^2 = 0.187$; $p < 0.001$).*

***Conclusions.** Following adjustment for age, sex, pubertal status, and clinical group, the independent association of IGF-1 with eNOS levels suggests its potential significance as an endocrine factor regulating endothelial function in children with COVID-19 and MIS-C.*

***Keywords:** Growth Hormone; IGF-1; eNOS; COVID-19; MIS-C; Children.*

Introduction

Modulation of endothelial nitric oxide synthase (eNOS) by growth hormone (GH) and insulin-like growth factor-1 (IGF-1) constitutes a fundamental mechanism for preserving vascular homeostasis and cardiovascular function [1-4]. Vascular effects of GH are largely mediated through stimulation of systemic and local IGF-1 production, which exerts direct effects on endothelial and endothelial progenitor cells (EPCs) [5]. Upon binding to the IGF-1 receptor (IGF-1R), IGF-1 triggers the intracellular phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling cascade. Subsequent phosphorylation of eNOS at serine residues by activated Akt enhances enzymatic activity and nitric oxide (NO) synthesis [2, 6]. IGF-1 further is able to enhance its vasoprotective effects by upregulating eNOS gene expression and increasing total cellular eNOS protein content [2, 7].

Evidence further indicates that GH may exert direct effects on the vascular system independent of IGF-1 via interaction with endothelial growth hormone receptors (GHRs) [8, 9]. GH–GHR complex formation activates the JAK2/STAT5 signaling pathway, which mediates genomic GH responses and is potentially involved in the regulation of eNOS expression. Concurrent activation of the PI3K/Akt pathway by GH provides an additional mechanism for stimulating eNOS activity and NO synthesis [8].

Clinical evidence demonstrates that recombinant GH therapy in patients with growth hormone deficiency restores NO bioavailability, reduces arterial stiffness, and mitigates overall cardiovascular risk [10, 11], underscoring the GH/IGF-1 axis as a critical regulator of endothelial function.

Although extensively characterized in adult cohorts and experimental in vitro models, these endocrine-vascular relationships remain poorly defined in pediatric populations, particularly during SARS-CoV-2 infection. Coronavirus disease 2019 (COVID-19) typically involves multiorgan pathology characterized by endothelial dysfunction, systemic inflammation, and endocrine perturbations, with somatotropic axis dysfunction and subsequent IGF-1 depletion representing a frequent clinical manifestation [12]. Multisystem inflammatory syndrome in children (MIS-C) warrants particular clinical attention, given the heightened severity of endothelial injury and systemic inflammatory response observed in this condition.

The aim of the study

The aim of the study was to determine the association between somatotropic axis markers, particularly GH and IGF-1 levels, and eNOS values in children with COVID-19 and MIS-C.

Materials and Methods

Ninety children were enrolled: 63 with coronavirus disease 2019 (COVID-19), 15 with MIS-C, and 12 controls without evidence of SARS-CoV-2 infection. Infection status was confirmed by polymerase chain reaction, antigen testing, or serological assays, with MIS-C diagnosis established according to World Health Organization criteria [13].

Participants aged 1 month to 17 years (mean 6.94 ± 5.61 years) showed no significant age differences among groups ($p > 0.05$) (Table 1). Of these, 55 were boys (61.11%) and 35 were girls (38.89%), with boys significantly more prevalent among patients with MIS-C ($p < 0.05$) (Table 1). Pubertal status, assessed by Tanner staging, did not differ significantly among groups ($p > 0.05$), with 54 children (60%) classified as prepubertal and 36 (40%) as pubertal (Table 1).

GH, IGF-1, and eNOS concentrations were quantified using enzyme-linked immunosorbent assay kits: hGH AccuBind ELISA Kit (Cat. No. 1725-300; Monobind Inc., USA), Human IGF-1 (Insulin-like Growth Factor 1) ELISA Kit (Cat. No. E-EL-H0086; Elabscience, USA), and Human NOS3/eNOS (Nitric Oxide Synthase 3, Endothelial) ELISA Kit (Cat. No. E-EL-H0755; Elabscience, USA).

Table 1

Clinical Characteristics of Patients in the Study Groups

Parameter	COVID-19	MIS-C	Control	p
Age, years (Mean±SD)	6.31 ± 5.77	7.54 ± 4.85	9.50 ± 5.16	p > 0.05
Sex, n (%)				χ^2=6.18; p=0.045*
Male	37 (58.73)	13 (86.67)	5 (41.67)	
Female	26 (41.27)	2 (13.33)	7 (58.33)	
Pubertal status, n (%)				χ^2=3.96; p=0.138
Prepubertal	42 (66.67)	7 (46.67)	5 (41.67)	
Pubertal	21 (33.33)	8 (53.33)	7 (58.33)	

*Note. * statistically significant result.*

Written informed consent was obtained from parents or legal guardians prior to enrollment. Conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Committee of I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine (Protocol No. 71, October 25, 2022), the study adhered to established ethical standards.

Statistical analysis was performed using IBM SPSS Statistics and GraphPad Prism software. Normally distributed quantitative variables were presented as mean and standard deviation (Mean±SD) and non-normally distributed variables were expressed as median and interquartile range (Me [Lq; Uq]).

Comparisons between two independent groups with non-normal distribution were conducted using the Mann–Whitney U test and among three groups via the Kruskal–Wallis test; correlation analysis was carried out by Spearman's rank correlation method. Categorical variables were presented as absolute numbers (n) and percentages (%); comparisons between two groups for qualitative variables were performed with the two-tailed Fisher's exact test, and among three groups by Pearson's χ^2 test. Multiple linear regression analysis was applied to determine the influence of potential predictors on eNOS levels. Differences were considered statistically significant at $p < 0.05$.

The study as part of the research project «Clinical phenotypes and pathogenetic mechanisms of COVID-19 and multisystem inflammatory syndrome in children, and risk stratification of post-COVID disorders in children with comorbid pathology» (UDC: 616.98:578.834.1-053.2:616-078:616-036.8; state registration No. 0126U000023; implementation period: 2026-2028).

Results and Discussion

Growth hormone levels across all study groups remained within the normal range [12], although median values varied: 1.53 (0.26; 3.59) ng/mL in children with COVID-19, 0.29 (0.10; 0.88) ng/mL in those with MIS-C, and 1.73 (0.64; 3.63) ng/mL in controls. The lowest GH concentrations were observed in the MIS-C group, yielding statistically significant intergroup differences ($H = 9.57$; $p = 0.008$).

IGF-1 concentrations in children with COVID-19 were 1.88-fold lower relative to controls [72.34 (39.15; 96.01) ng/mL vs. 135.97 (101.96; 194.45) ng/mL; $p < 0.05$], with an even more pronounced reduction in the MIS-C group, where levels were 5.60-fold lower than controls [24.29 (16.41; 38.83) ng/mL; $p < 0.05$]. These findings resulted in highly significant overall intergroup differences ($H = 29.34$; $p < 0.001$ Notably, IGF-1 levels below the normal range were identified in 27 children (30.0%), all of whom had confirmed SARS-CoV-2 infection.

Low GH and IGF-1 levels may reflect endocrine dysregulation related to the involvement of the hypothalamic-pituitary system while concurrently contributing to impaired antiviral immunity. Both GH and IGF-1 support proliferation and differentiation of T and B lymphocytes, maintain thymic function, enhance natural killer cells, macrophages, and phagocytes, activity and modulate cytokine production [14-16]. Reduced GH and IGF-1 concentrations further serve as important biomarkers for cardiovascular morbidity, being associated with elevated cardiometabolic risk, disrupted vascular homeostasis, and endothelial dysfunction development [17-19].

The levels of eNOS, regarded as a marker of endothelial dysfunction, were significantly lower in

children with COVID-19 (484.90 [415.70; 626.00] pg/mL) and MIS-C (328.32 [289.23; 405.80] pg/mL) relative to uninfected controls (691.75 [594.80; 909.15] pg/mL) (H=25.14; p<0.001), findings that align with prior studies demonstrating reduced eNOS expression and diminished nitric oxide bioavailability in SARS-CoV-2 infection [20-22].

Lower GH and IGF-1 levels correlated with reduced eNOS values, as indicated by significant positive correlations between these parameters (p<0.05) (Figure 1). This association accords with experimental evidence implicating the somatotropic axis in endothelial function regulation via PI3K/Akt/eNOS signaling pathway activation and enhanced nitric oxide bioavailability [8].

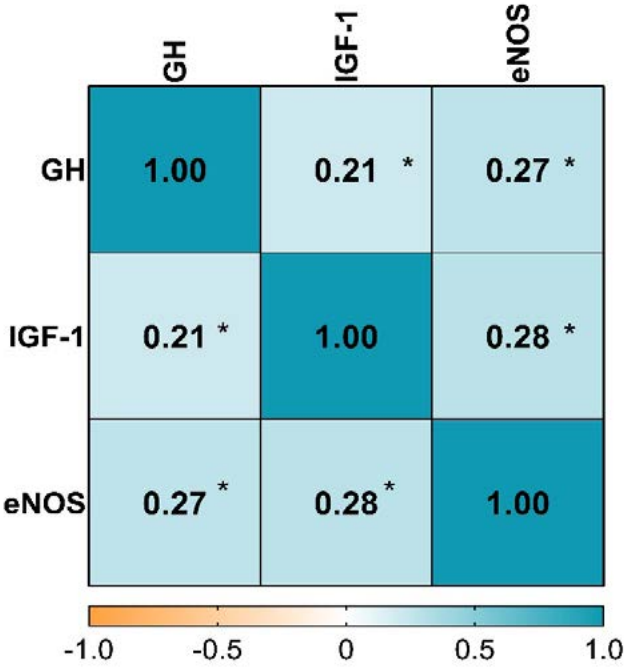

Figure 1. Relationship between somatotropic axis markers (GH and IGF-1) and eNOS levels.
(statistically significant result)*

Given the observed reduction in IGF-1 levels among SARS-CoV-2-infected individuals, eNOS concentrations were analyzed according to IGF-1 status in patients with COVID-19 and MIS-C, revealing that low IGF-1 levels were significantly associated with lower eNOS values in children infected with SARS-CoV-2 (p = 0.008) (Figure 2).

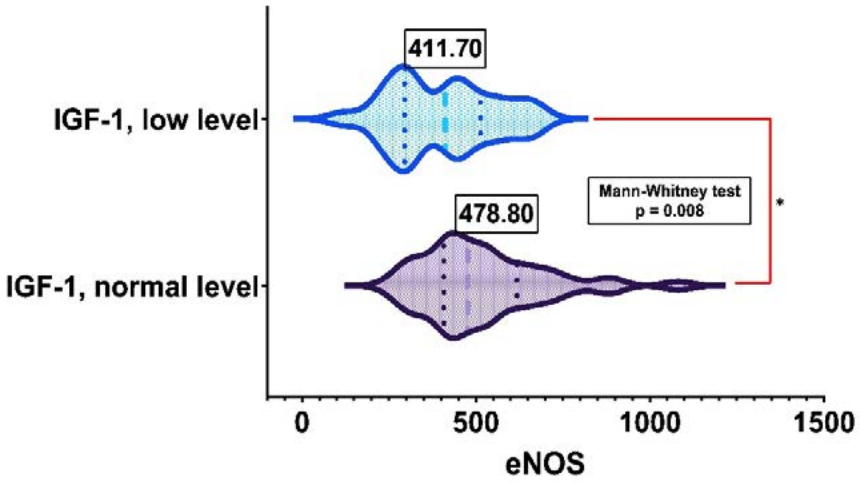

Figure 2. eNOS levels according to IGF-1 values in children.
(statistically significant result)*

To evaluate the contribution of the somatotropic axis to the endothelial response, specifically its effect on eNOS concentrations in children with COVID-19 and MIS-C, multiple linear regression analysis was performed with eNOS designated as the dependent variable and age, sex, pubertal status, clinical group (COVID-19, MIS-C, control), GH, and IGF-1 specified as potential predictors. To address multicollinearity between GH and IGF-1, these biomarkers were incorporated into separate models (Model 1: GH; Model 2: IGF-1), a design that isolated the independent contribution of each hormone to eNOS variability within the pediatric cohort.

Although the GH-inclusive model failed to achieve overall statistical significance ($R = 0.286$; $R^2 = 0.082$; adjusted $R^2 = 0.022$; $p = 0.250$), growth hormone itself exhibited a weak yet statistically significant positive association with eNOS levels ($\beta = 0.23$; $B = 30.55$; $p = 0.048$), whereas the remaining covariates – age ($p = 0.809$), sex ($p = 0.598$), clinical group ($p = 0.144$), and pubertal status ($p = 0.651$)— exerted no statistically significant effects (Table 2).

Table 2

Results of Multiple Linear Regression Analysis of Predictors of eNOS Levels: Model 1 Including Growth Hormone

Predictor	β	Standard Error of β	B	Standard Error of B	t	p
Constant			393.83	78.94	4.99	< 0.001*
Age, years	0.07	0.28	2.41	9.94	0.24	0.809
Sex (male / female)	0.06	0.11	24.66	46.54	0.53	0.598
Pubertal status	–0.13	0.28	–51.67	113.60	–0.45	0.651
Clinical group (COVID-19 / MIS-C / Control)	0.17	0.11	20.24	13.71	1.48	0.144
Growth hormone, ng/mL	0.23	0.11	30.55	15.18	2.01	0.048*

*Note. * statistically significant result.*

The absence of statistical significance in the model including GH, notwithstanding the positive association between GH and eNOS levels, likely reflects constraints of single-time-point GH quantification in SARS-CoV-2-infected children; given the hormone's pulsatile secretory profile, isolated measurements may inadequately capture its biological effect on endothelial function [23]. The statistically significant association between GH and eNOS nonetheless substantiates the potential role of GH in maintaining endothelial function via direct effects on the vascular endothelium and activation of PI3K/Akt signaling pathways [24].

The IGF-1-inclusive model achieved statistical significance ($R = 0.487$; $R^2 = 0.237$; adjusted $R^2 = 0.187$; $p < 0.001$), with the specified predictors accounting for 18.7% of eNOS level variability. Regression analysis revealed that increased IGF-1 concentration correlated with elevated eNOS levels ($\beta = 0.50$; $B = 1.94$; $p < 0.001$), implying that the reduced IGF-1 concentrations observed in COVID-19 and MIS-C correspond to diminished eNOS values. Within this model, however, –age, sex, pubertal status, and clinical group – failed to demonstrate statistically significant associations with eNOS levels ($p > 0.05$) (Table 3).

Table 3

Results of Multiple Linear Regression Analysis of Predictors of eNOS Levels: Model 2 Including IGF-1

Predictor	β	Standard Error of β	B	Standard Error of B	t	p
Constant			411.11	67.98	6.05	< 0.001*
Age, years	0.01	0.26	0.10	9.00	0.01	0.991
Sex (male / female)	–0.02	0.10	–8.58	43.27	–0.20	0.843
Pubertal status	–0.25	0.26	–102.77	104.32	–0.99	0.328
Clinical group (COVID-19 / MIS-C / Control)	0.04	0.10	5.43	12.72	0.43	0.671
IGF-1, ng/mL	0.50	0.11	1.94	0.43	4.50	< 0.001*

*Note. * statistically significant result.*

Comparative analysis of the two models indicated a stronger association between IGF-1 and eNOS levels relative to GH, the IGF-1-inclusive regression model demonstrating nearly threefold greater explanatory power ($R^2 = 0.237$ vs. 0.082) while achieving statistical significance. These findings underscore the utility of IGF-1 measurement as an indicator of somatotropic axis functional status, given that IGF-1 exhibits greater stability, a longer half-life, and reduced susceptibility to fluctuations driven by other biological factors [23, 25].

The absence of statistically significant clinical determinants across both predictive models underscores the predominant influence of endocrine factors in determining eNOS levels in children with COVID-19 and MIS-C, suggesting that IGF-1 may be regarded as an independent biological marker of endothelial dysfunction in pediatric patients with SARS-CoV-2-associated conditions.

Conclusions

The peripheral component of the somatotropic axis, represented by IGF-1, plays an important role in maintaining endothelial function in children with SARS-CoV-2-associated diseases. The independent association of IGF-1 with eNOS levels, identified following adjustment for age, sex, pubertal status, and clinical group, suggests its potential role as an endocrine regulator of endothelial function in children with COVID-19 and MIS-C.

Perspectives for Future Research

Given the multifaceted impact of GH and IGF-1 and their established involvement in the development of endothelial dysfunction in COVID-19 and MIS-C, incorporating IGF-1 assessment into the diagnostic evaluation of children with MIS-C warrants consideration. Furthermore, monitoring IGF-1 levels in children following SARS-CoV-2 infection could facilitate identification of potential long-term cardiovascular sequelae and inform strategies to address concurrent hormonal-endothelial imbalances.

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ВЗАЄМОЗВ'ЯЗОК СОМАТОТРОПНОЇ ОСІ ТА ЕНДОТЕЛІАЛЬНОЇ СИНТАЗИ ОКСИДУ АЗОТУ У ДІТЕЙ ІЗ COVID-19 ТА МУЛЬТИСИСТЕМНИМ ЗАПАЛЬНИМ СИНДРОМОМ

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Резюме.

Вплив гормону росту (ГР) та інсуліноподібного фактора росту-1 (ІФР-1) на ендотеліальну синтазу оксиду азоту (eNOS) розглядають як один із важливих механізмів підтримання судинного гомеостазу і функціонального стану серцево-судинної системи. У дітей із COVID-19, особливо при мультисистемному запальному синдромі (MIS-C), можливе поєднання ендотеліальної дисфункції та порушень соматотропної осі, однак ці взаємодії залишаються недостатньо вивченими.

Мета дослідження: встановити особливості взаємозв'язку між рівнями ГР, ІФР-1 та значеннями eNOS у дітей із COVID-19 та MIS-C.

Матеріали і методи дослідження. Дослідженням охоплено 90 дітей віком від 1 місяця до 17 років, серед яких 63 пацієнти з COVID-19, 15 дітей із MIS-C та 12 дітей контрольної групи без ознак інфікування SARS-CoV-2. Визначення ГР, ІФР-1 та eNOS проводили з використанням імуноферментних тест-систем – hGH AccuBind ELISA Kit (Cat. No: 1725-300; Monobind Inc., USA), Human IGF-1(Insulin-like Growth Factor 1) ELISA Kit (Cat. No: E-EL-H0086; Elabscience, USA), Human NOS3/eNOS (Nitric Oxide Synthase 3, Endothelial) ELISA Kit (Cat. No: E-EL-H0755E-EL-H0755; Elabscience, USA). Дослідження схвалено комісією з біоетики Тернопільського національного медичного університету імені І. Я. Горбачевського Міністерства охорони здоров'я України (протокол № 71 від 25 жовтня 2022 р.). Статистичний аналіз проводили з використанням програмного забезпечення IBM SPSS Statistics та GraphPad Prism. Статистично значущими вважали відмінності при $p<0,05$. Науково-дослідна робота «Клінічні фенотипи та патогенетичні механізми перебігу COVID-19 і мультисистемного запального синдрому у дітей та стратифікація ризику постковідних порушень у дітей з коморбідною патологією», УДК: 616.98:578.834.1-053.2:616-078:616-036.8, № держ. реєстрації 0126U000023, терміни виконання 2026-2028 рр.

Результати дослідження. Зниження рівнів ГР та ІФР-1 асоціювалося з нижчими значеннями eNOS, що підтверджувалося достовірними позитивними кореляційними зв'язками між цими показниками ($p<0,05$): $r_{гр\text{-}eNOS}=0,27$; $r_{ІФР\text{-}1\text{-}eNOS}=0,21$. Низький рівень ІФР-1 супроводжувався достовірно нижчими значеннями eNOS у дітей, інфікованих SARS-CoV-2, порівняно з пацієнтами з нормальним рівнем ІФР-1 ($p=0,008$): 411,70 (300,90; 499,80) нг/мл і 478,80 (413,60; 622,70) нг/мл відповідно. За результатами множинного лінійного регресійного аналізу предикторів рівня eNOS модель, що включала ГР, не досягла статистичної значущості (adjusted $R^2=0,022$; $p=0,250$), хоча ГР продемонстрував слабкий незалежний позитивний зв'язок із рівнем eNOS ($\beta=0,23$; $B=30,55$; $p=0,048$). Натомість модель, що включала ІФР-1, показала, що підвищення концентрації ІФР-1 асоціювалося зі зростанням рівня eNOS ($\beta=0,50$; $B=1,94$; $p<0,001$), а сама модель була статистично значущою (adjusted $R^2=0,187$; $p<0,001$).

Висновки. Незалежна асоціація ІФР-1 із рівнем eNOS після корекції на вік, стать, пубертатний статус та клінічну групу свідчить про його потенційне значення як ендокринного чинника регуляції ендотеліальної функції у дітей із COVID-19 та MIS-C.

Ключові слова: гормон росту; ІФР-1; eNOS; COVID-19; MIS-C; діти.

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