International Journal of Advanced Biochemistry Research

ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2025; 9(3): 179-182
www.biochemjournal.com
Received: 15-12-2024
Accepted: 18-01-2025

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The interplay of mineral homeostasis and inflammatory biomarkers in the pathogenesis of juvenile hypertension: A case-control study

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DOI: https://www.doi.org/10.33545/26174693.2025.v9.i3c.3908

Abstract
Biochemical alterations often accompany multi-organ damage, a condition primarily induced by hypertension. This study investigated plasma levels of total protein, albumin, C-reactive protein (CRP), and trace elements (Mn, Ca, Zn, Se, Mg, Fe) in juvenile hypertensive patients (n=30) compared to normotensive controls (n=30) in Ekiti State, Nigeria. Venous blood samples were collected after overnight fasting, and plasma was analyzed using standard methods. No significant differences (p>0.05) were observed in total protein, albumin, Mn, Zn, or Fe. However, juvenile hypertensive patients exhibited significantly higher CRP (p<0.05), Ca (p<0.05), and Se (p<0.05), and significantly lower Mg (p<0.05) compared to controls. These findings suggest the presence of inflammation and altered mineral homeostasis in juvenile hypertension, potentially contributing to its etiology and informing management strategies.

Keywords: Albumin, total protein, C-reactive protein, minerals, juvenile hypertension

Introduction
Hypertension, characterized by the persistent elevation of arterial blood pressure, constitutes a significant global health burden. Defined clinically as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (Unger *et al*., 2020) [23], hypertension often presents asymptomatically, contributing to its insidious nature and association with severe cardiovascular and renal complications (W.H.O., 2023) [25]. Specifically, hypertension is recognized as a critical risk factor for cerebrovascular accidents, dementia, cardiovascular disease, and chronic kidney disease (Zhou *et al*., 2015) [28]. Recent research has highlighted the increasing prevalence of juvenile hypertension and its potential association with early-onset cardiovascular and renal pathologies (Flynn *et al*., 2017; Leiba *et al*., 2019; Yang *et al*., 2020) [8, 14, 26]. Notably, contemporary lifestyle and nutritional factors are hypothesized to contribute to an elevated risk of cardiovascular complications in younger populations compared to older demographics (Redwine *et al*., 2012; Al-Huthi *et al*., 2023) [21, 1].
Juvenile hypertension, diagnosed based on age-, sex-, and height-adjusted blood pressure percentiles, differs significantly from adult hypertension. Normal blood pressure ranges in pediatric populations vary from 60-80/30-50 mmHg in neonates to 90-120/60-80 mmHg in adolescents aged 13-18 years.
Plasma proteins, including albumin and globulins, play crucial roles in physiological homeostasis. Albumin, the most abundant plasma protein, is essential for the transport of hydrophobic substances, while globulins contribute to immune responses and infection control. Additionally, plasma proteins regulate fluid distribution across vascular compartments. Consequently, alterations in plasma protein levels, specifically total protein and albumin, serve as diagnostic markers for various pathological conditions, including hypertension, diabetes, inflammation, and organ dysfunction. C-reactive protein (CRP), a sensitive marker of systemic inflammation, is an acute-phase protein that exhibits a rapid increase in response to tissue injury, infection, or inflammation (Sesso *et al*., 2007; Wang *et al*., 2003) [22, 24]. C-reactive protein (CRP) is found in blood, the levels of which rise in response to inflammatory CRP in an acute phase protein. CRP is synthesized by the liver in response to factors released by macrophages and fat cells (Oyeyemi & Asaolu, 2015) [20].

It's physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via the carrier (CLQ) complex (Oyeyemi & Asaolu, 2015) [20]. Measuring CRP level is a screen for infections and inflammatory diseases. Elevated CRP levels have been implicated in the pathogenesis of hypertension, potentially through the inhibition of endothelial nitric oxide production and subsequent vasoconstriction (Boos & Lip, 2005) [5].

Furthermore, trace elements are essential for physiological processes, including enzymatic reactions and tissue maintenance. Dysregulation of these elements may contribute to the development and progression of hypertension.

This study aims to evaluate plasma levels of total proteins, albumin, CRP, and selected trace elements in juvenile hypertensive patients and normotensive controls to elucidate their potential roles in the pathogenesis of juvenile hypertension."

Materials and Methods

Subjects

A case-control study was conducted, recruiting thirty (30) newly diagnosed juvenile hypertensive patients (≤18 years) from Ekiti State Teaching Hospital (EKSUTH) and Federal Teaching Hospital, Ido-Ekiti (FETHI) (Group A). Thirty (30) normotensive juvenile controls, matched for age, were also recruited. Patients receiving antihypertensive medication were excluded.

Data collection

The ethical clearance was sought from Ethics and Research Committee of Ekiti State Teaching Hospital, Ado-Ekiti, Nigeria (approval number: EKSUTH/A67/2024/01/001). Informed consent was obtained from the participants (subjects and control) after the study guidelines had been explained to them before clinical history was taken and anthropometric indices using structured questionnaire.

Sample collection and Preparation

Venous blood (5 ml) was collected from each participants into ethylenediaminetetraacetic acid (EDTA) bottles which were then centrifuged at 10,000 rpm for 10 minutes to obtain plasma.

Biochemical Analysis

"Plasma albumin concentrations were determined spectrophotometrically employing the dye-binding method, as described by Cheesbrough (1999) [6]. Total protein concentrations were quantified using the Biuret method, following the protocol outlined by Cheesbrough (1999) [6]. Trace element concentrations, including calcium (Ca), iron (Fe), zinc (Zn), selenium (Se), and manganese (Mn), were determined using atomic absorption spectroscopy. Plasma magnesium (Mg) levels were estimated utilizing Agape Reagents on a ChemRay-240 Analyzer."

Statistical Analysis

"Statistical analysis was performed using SPSS version 20.0. Data are presented as mean±standard error of the mean (SEM). The significance of differences between group means was assessed using Student's t-test. Pearson's correlation coefficient was calculated to determine the strength and direction of linear relationships between variables.

Table 1: Anthropometric and Blood Pressure Characteristics of Juvenile Normotensive and Hypertensive Subjects

Parameter	Range	Control (Mean ± SEM)	Hypertensive (Mean ± SEM)	*p*-value
Age (years)	3-15	8.15±3.65	6.77±3.31	0.171
Height (m)	1.04-1.50	1.17±0.18	1.11±0.13	0.166
Weight (kg)	16-34	26.30±7.17	24.40±6.41	0.303
Waist (cm)	12-32	21.30±6.23	23.13±5.91	0.298
SBP (mmHg)	90-140	100.75±6.74	127.73±7.00	0.0001*
DBP (mmHg)	30-100	71.50±6.50	88.13±12.19	0.0001*

Note: Values are presented as Mean ± SEM (n=30). $p<0.05$ indicates statistical significance. SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.

Table 2: Plasma Levels of Biochemical Parameters and Trace Elements in Juvenile Normotensive and Hypertensive Subjects

Parameter (Units)	Control (Mean ± SEM)	Hypertensive (Mean ± SEM)	*p*-value
TP (g/L)	58.55±1.58	58.07±0.96	0.783
ALB (g/L)	43.00±1.40	42.23±0.93	0.635
CRP (mg/L)	3.30±1.89	12.00±2.91	0.001*
Ca (mg/L)	11.98±0.92	15.42±1.03	0.023*
Mn (mg/L)	0.0002±0.0001	0.0014±0.001	0.283
Fe (mg/L)	0.21±0.03	0.35±0.07	0.080
Zn (µg/dL)	108.80±19.37	80.90±38.42	0.055
Se (µg/L)	102.70±22.05	180.10±14.26	0.001*
Mg (mg/dL)	1.98±0.20	0.65±0.39	0.001*

Note: Values are presented as Mean ± SEM (n=30). $p<0.05$ indicates statistical significance. TP = Total Protein; ALB = Albumin; CRP = C-Reactive Protein.

Discussion

"Cardiovascular complications, which contribute significantly to global mortality and morbidity, are often associated with elevated arterial blood pressure. Understanding the metabolic processes that predispose individuals to this condition and its severity is crucial for mitigating associated complications. In this study, no significant differences were observed in body weight and waist circumference between juvenile hypertensive and normotensive subjects. As demonstrated in Table 1, systolic and diastolic blood pressures were significantly elevated in the hypertensive group ($p<0.05$). These findings suggest that the observed blood pressure elevations were independent of weight and waist circumference in this cohort.

Table 2 illustrates that plasma total protein and albumin levels did not differ significantly between the hypertensive and normotensive groups ($p<0.05$). This indicates that the observed blood pressure elevations did not significantly affect these protein levels. This result supports previous findings in pediatric hypertension, which reported no correlation between elevated blood pressure and alterations in total protein or serum albumin (Okuda *et al*., 2019) [19]. Conversely, other studies have suggested that factors such as insulin resistance or obesity may exert a greater influence on total protein and serum albumin levels (Liu *et al*., 2024) [15]. The present study aligns with these reports, suggesting that juvenile hypertension may not directly impact plasma protein levels but may be influenced by broader metabolic health.

Plasma C-reactive protein (CRP) levels were significantly elevated in hypertensive subjects ($p<0.05$), indicating systemic inflammation. This finding is consistent with previous research demonstrating the involvement of systemic inflammation in the pathogenesis of elevated

arterial blood pressure (Kramer *et al*., 2019; Nehring *et al*., 2023) [12, 18]. Additionally, metabolic syndromes have been associated with elevated CRP levels in children and adolescents, although these associations may be influenced by ethnicity, sex, and age (Lande *et al*., 2008) [13]. These results collectively suggest a strong association between juvenile hypertension and systemic inflammation.

A significant decrease in serum magnesium levels was observed in hypertensive subjects ($p<0.05$). This reduction may be attributed to inadequate dietary magnesium intake, increased urinary excretion, medication-induced sodium excretion, or chronic stress (Ho *et al*., 2016) [10]. Previous studies have linked decreased magnesium levels with increased vascular resistance, vasoconstrictor sensitivity, and endothelial dysfunction (AlShanableh & Ray, 2024) [2]. Furthermore, hypomagnesemia has been associated with both hypertension and prehypertension, suggesting its potential role in juvenile hypertension (Guerrero-Romero *et al*., 2016; Kass & Sullivan, 2016) [9, 11]. These findings underscore the importance of monitoring electrolyte balance in the management of elevated arterial blood pressure, as decreased magnesium levels may indicate underlying metabolic disturbances.

Manganese, zinc, and iron levels did not differ significantly between the two groups ($p<0.05$). While cohort studies have reported varying associations between manganese levels and arterial blood pressure, evidence linking hypertension directly to manganese levels remains limited (Nahed *et al*., 2019) [16]. Similarly, although zinc deficiency has been implicated in various health conditions, its direct relationship with hypertension is not well-established (Zhao *et al*., 2023; Nasir *et al*., 2024) [27, 17]. These results suggest that these minerals may not exert a direct influence on juvenile hypertension.

Conversely, calcium and selenium levels were significantly elevated in hypertensive subjects ($p<0.05$). Increased calcium levels may be attributed to dietary supplementation or reflect adaptive or maladaptive renal or vascular responses that alter calcium homeostasis (Chiu *et al*., 2021) [7]. Changes in the renin-angiotensin-aldosterone system (RAAS) and parathyroid hormone regulation have also been implicated (Bastola *et al*., 2020; Anamika *et al*., 2023) [4, 3]. Elevated selenium levels may reflect increased oxidative stress, a condition associated with hypertension, where selenium acts as a compensatory antioxidant (Bastola *et al*., 2020) [4].

Conclusion

This study demonstrates that juvenile hypertension is associated with altered mineral homeostasis and systemic inflammation."

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