Pediatric Hypertension: A Study on the Correlation with Biochemical Markers

Fengsong Yang[1],*

[1]*Department of Laboratory Medicine, The First People's Hospital of Anning City Affiliated with Kunming University of Science and Technology, Anning, Yunnan, 650300, China*
*Corresponding author

Abstract: The aim of this study is to investigate the prevalence of hypertension and associated biochemical markers in children and adolescents in China, with a view to informing early intervention strategies to prevent cardiovascular disease (CVD) and reduce related mortality. A cross-sectional study was conducted from June 1, 2020, to October 31, 2022, including 73 students aged 8 to 12 from Anning City, Yunnan Province. Participants, spanning grades 3 to 6, were enrolled with guardian consent. Blood pressure and lipid profiles were the primary metrics. Hypertension categorization followed the 4th Report by the American Academy of Pediatrics and the European Society of Hypertension's 2009 guidelines, with local guidelines for pediatric hypertension also considered. Data on clinical history, physical measurements, and laboratory analyses were compiled, including five blood pressure readings over three days. Fasting blood samples were analyzed for total cholesterol, triglycerides, HDL, and LDL using a Hitachi 008AS biochemical analyzer. Results of the study indicated a distribution within the cohort as follows: normotensive status in 60.2%, prehypertension in 32.9%, and hypertension in 6.9%. Significant differences in total cholesterol, triglycerides, and LDL across blood pressure categories were observed($p<0.005$), with higher lipid levels correlating with increased hypertension severity. The LDL/HDL ratio was significantly higher in the hypertensive group($p=6.56^{e-07}$). Elevated lipoprotein(a) levels and ApoB/ApoA ratios in hypertensive children pointed to these markers as strong indicators of cardiovascular disease risk. This study highlights a concerning prevalence of prehypertension and hypertension in Chinese children, with significant associations between elevated blood pressure and lipid abnormalities. These findings underscore the need for early monitoring and intervention to address CVD risk in pediatric populations.

1. Introduction

Globally, cardiovascular disease (CVD) remains a significant source of morbidity and is projected to be the leading cause of death, with an anticipated increase to over 23.6 million fatalities annually by 2030[1]. This escalation underscores the urgent need for enhanced prevention and management strategies worldwide. Notably, CVD is the primary cause of mortality in both China and high-income

countries, and its prevalence is similarly rising in various middle- and low-income nations[2].

Atherosclerosis, characterized by the pathological deposition of lipids, cholesterol, and plaque within the arterial walls, leads to coronary artery disease and other cardiovascular conditions. This process is multifactorial, with a broad spectrum of identified risk factors[3]. Alarmingly, atherosclerosis is manifesting at younger ages, emphasizing the importance of early health status assessments in relation to its principal causative factors. Such evaluations are crucial for the early implementation of both preventive and therapeutic interventions, aiming to curtail the progression or alleviate the consequences of this disease.

The primary risk factors for cardiovascular disease include hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, genetic predispositions, and a family history of CVD. These factors highlight the complex interplay of lifestyle, environmental, and genetic components in the pathogenesis of CVD, necessitating a multifaceted approach to its prevention and treatment[4].

The interplay and cumulative impact of cardiovascular risk factors significantly influence an individual's susceptibility to cardiovascular disease. Epidemiological and clinical research has illuminated that the presence of multiple concurrent risk factors exponentially elevates the risk for cardiovascular disease compared to the presence of a solitary risk factor[5]. The co-occurrence of dyslipidemia (indicative of atherosclerotic disease) with hypertension underscores the augmented risk and highlights the imperative need for the assessment of pertinent biochemical markers.

Lifestyle behaviors and attitudes developed during childhood and perpetuated across the lifespan significantly contribute to the establishment of risk factors[6]. Consequently, the initiation of preventive measures against cardiovascular risk is critically necessary during childhood and adolescence. The past few decades have seen a burgeoning interest in identifying predisposing factors in children and adolescents for cardiovascular disease, advocating for these demographics to be included in primary prevention strategies.

Hypertension (HT) stands as one of the most prevalent conditions globally among adults, with its incidence escalating with age and serving as a substantial risk factor for cardiovascular disease. The repercussions of HT are grave, encompassing damage to the heart, blood vessels, kidneys, and retina. Despite common misconceptions, HT is not infrequent in the pediatric population; its global prevalence is estimated to range from 1% to 3% in children and up to 3.2% in adolescents[7]. According to the "China Cardiovascular Health and Disease Report 2020," the prevalence of hypertension among children and adolescents aged 7 to 17 years in China was reported at 20.5% in 2015[8].

The current consensus within the medical community posits that the initiation and progression of atherosclerosis are intimately linked to inflammatory processes within the vasculature[9]. Recent research endeavors have concentrated on delineating a spectrum of biochemical markers, including angiogenic growth factors, platelet activation phenomena, and thrombotic components associated with lipids and other elements[3,10]. Evidence increasingly supports that both local and systemic inflammatory indicators are pivotal in the atherosclerotic trajectory. A subset of these markers has been acknowledged as independent predictors for atherosclerosis and cardiovascular disease (CVD), rendering them invaluable for screening, diagnostic, and monitoring applications[7].

The oxidative modification of low-density lipoproteins (LDL) within the subendothelial layer plays a crucial role in vascular injury. LDL particles traverse endothelial cells and amass within the vascular intima, undergoing oxidative, glycosylative, acetylation, and triglyceride-enrichment processes that enhance their atherogenic potential[3,10].

Oxidized LDL particles exert atherogenic effects, a trait shared by other lipoproteins such as very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and lipoprotein(a). The genesis of atheroma plaque is an intricate inflammatory cascade, involving an array of cells and mediators. Oxidized lipoproteins, once infiltrated into the subendothelial space, incite intimal cells to

emit proinflammatory cytokines and chemokines. These signals activate circulating monocytes, which infiltrate the tissue, transform into inflammatory macrophages, and subsequently foam cells, culminating in the intracellular build-up of cholesterol esters and the development of fatty streaks[3,10].

The objective of this investigation is to highlight the notably elevated prevalence of hypertension (HT) among China children and adolescents, often concomitant with anomalous biochemical marker levels that prognosticate elevated CVD risk. A primary impetus is the prevention of early-onset CVD and curtailing mortality attributed to this condition in China.

2. Methods

2.1 Study Design and Participant Selection

From June 1, 2020, to October 31, 2022, a cross-sectional investigation was carried out involving 73 students, aged between 8 to 12 years, from educational institutions in Anning City, Yunnan Province, China, selected due to logistical convenience. The study encompassed children from grades 3 to 6, contingent upon receiving written informed consent from their guardians.

2.2 Measurement Variables

The primary metrics of this study encompass blood pressure levels, body anthropometrics (weight and height), and a detailed lipid profile.

2.3 Blood Pressure Assessment

For the categorization of hypertension (HT), the study employed the criteria set forth in the 4th Report by the American Academy of Pediatrics[2] and the guidelines issued by the European Society of Hypertension in September 2009[11]; For the diagnosis of pediatric hypertension, refer to the guidelines outlined in the "Research Progress on the Diagnosis and Treatment of Hypertension in Children" from China[12]. Participants were deemed normotensive if both average systolic and diastolic pressures fell below the 90th percentile; prehypertensive if average systolic and/or diastolic pressures were at or above the 90th but below the 95th percentile; and hypertensive if either average systolic or diastolic pressure met or exceeded the 95th percentile, with all percentiles adjusted for age, gender, and height.

2.4 Lipid Panel Biochemical Markers

Assessments included cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), lipoprotein (a) [Lp(a)], apolipoprotein A (ApoA), and apolipoprotein B (ApoB), along with calculated ratios of cholesterol/HDL, LDL/HDL, and ApoB/ApoA.

2.5 Data Collection and Processing

The compilation of data incorporated clinical histories, physical measurements, and laboratory analyses. Recorded data included blood pressure, weight, height, and lipid profile outcomes. Blood pressure was measured five times across three days.

For the laboratory analyses, subjects were instructed to fast for 12 hours prior to the venipuncture. Guardians were informed to ensure adherence to this requirement. Blood samples were drawn from the antecubital vein, with serum isolated following coagulation and centrifugation at 3000 rpm for 15 minutes. Serum levels of total cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-c), and LDL cholesterol (LDL-c) were measured using a Hitachi clinical automatic biochemical analyzer,

model 008AS. Results were expressed in mg/dL.(Tab 1)[13,14]

Table 1: Reference Values for Hematological and Biochemical Parameters in Adolescents

Parameter	Ideal (mg/dL)	Normal range (mg/dL)	Dyslipidemia (mg/dL)
Triglycerides			
0–9 years	<75	75–99	≥100
10–19 years	<90	90-129	≥130
TC	<170	170–199	≥200
LDL-c	<110	110–129	≥130
HDL-c	>45	40–45	<40
Markers			
TC/HDL ratio		≤3.5	
LDL/HDL ratio		≤2.2	
Apolipoprotein - A1 (ApoA)		>130 mg/dL	
Apolipoprotein B-100 (ApoB)		90–140 mg/dL	
ApoB/ApoA ratio		0.8–1.2	
Lipoprotein(a)		>25 mg/dL	

Note: TC: total cholesterol LDL-c: low-density lipoprotein HDL-c: high-density lipoprotein

3. Analysis

Statistical analysis was conducted using R software, version 4.3. The descriptive statistics employed encompassed means and standard deviations for each grouping within the lipid profile biochemical markers. For qualitative variables, independence was tested using the chi-square statistic and its associated p-value, while quantitative variables were analyzed using mean comparison tests, including ANOVA and its nonparametric counterpart, the Kruskal-Wallis test. The threshold for statistical significance was set at $p = 0.05$.

4. Ethics

Informed consent was obtained from the parents of the participating children after a thorough explanation of the study's aims, and the associated risks and benefits, in accordance with the ethical principles of the Declaration of Helsinki and WHO guidelines. In compliance with Cuban regulations, which necessitate the involvement of the Ministry of Education for research involving schoolchildren, the requisite authorization was secured. All collected data was maintained in strict confidence, ensuring that no child's identity was ever revealed. The selection of diagnostic methods was guided by material availability, a commitment to optimizing participant benefit, adherence to the ethical principle of non-maleficence, and in line with both international and national standards for good clinical and laboratory practice.

Parents of the children who participated in the study were duly informed of the results from physical examinations and diagnoses derived from clinical and biochemical data. Should there be any abnormalities detected in the blood biochemical tests, parents were advised to seek further medical attention for their child at the Anning City First People's Hospital's pediatric department.

5. Results

5.1 Distribution of Blood Pressure Categories among Study Participants

In the studied cohort, the distribution of blood pressure categories was as follows: 60.2% (n=44) of the subjects were classified within the normotensive group, 32.9% (n=24) were identified as

prehypertensive, and 6.9% (n=5) were categorized as hypertensive, with the total number of participants being 73, accounting for 100% of the sample population.(Table 2).

Table 2: Baseline Blood Pressure Characteristics of Study Subjects (n, %)

Blood pressure category	Frequency(n)	Percentage (%)
Normotensive Group	44	60.2
Prehypertension Gr oup	24	32.9
Hypertension Group	5	6.9
Total	73	100

5.2 Assessment of Biochemical Indicators across Blood Pressure Categories

Table 3: Comparison of Biochemical Values Across Different Blood Pressure Groups($\bar{x} \pm s$)

Variable	Category	n	$\bar{x} \pm s$	Fisher's F	p
Cholesterol(mg/dL)	Normotensive Group	44	128.85±25.47		
	Prehypertension Group	24	140.14±22.60	6.35	2.93^{e-03}
	Hypertension Group	5	158.77±25.58		
Triglycerides(mg/dL)	Normotensive Group	44	87.47±38.20		
	Prehypertension Group	24	72.4±20.52	13.69	1.09^{e-03}
	Hypertension Group	5	158.55±37.40		
HDL(mg/dL)	Normotensive Group	44	47.35±10.56		
	Prehypertension Group	24	41.34±4.83	4.84	0.0107
	Hypertension Group	5	38.84±4.89		
LDL(mg/dL)	Normotensive Group	44	74.63±18.47		
	Prehypertension Group	24	86.61±27.65	11.85	3.69^{e-05}
	Hypertension Group	5	122.67±13.61		
Cholesterol/HDL	Normotensive Group	44	3.96±0.19		
	Prehypertension Group	24	3.00±0.44	11.43	5.06^{e-05}
	Hypertension Group	5	3.97±0.51		
LDL/HDL	Normotensive Group	44	1.55±0.74		
	Prehypertension Group	24	2.08±0.70	17.57	6.56^{e-07}
	Hypertension Group	5	3.47±0.68		
Lipoprotein(a)(mg/dL)	Normotensive Group	44	11.95±8.02		
	Prehypertension Group	24	13.23±6.27	6.5	2.57^{e-03}
	Hypertension Group	5	26.69±14.99		
ApoA(mg/dL)	Normotensive Group	44	136.912±8.16		
	Prehypertension Group	24	133.75±9.14	14.82	4.28^{e-06}
	Hypertension Group	5	114.36±7.63		
ApoB(mg/dL)	Normotensive Group	44	79.46±30.04		
	Prehypertension Group	24	90.93±40.14	3.14	0.0478
	Hypertension Group	5	115.91±53.92		
ApoB/ApoA	Normotensive Group	44	0.58±0.26		
	Prehypertension Group	24	0.76±0.28	17.59	6.47^{e-07}
	Hypertension Group	5	1.30±0.30		

Upon examining the biochemical markers across blood pressure categories, significant differences were discerned. Total cholesterol, triglycerides, and LDL values increased with higher blood pressure categories, with the hypertensive group displaying the highest levels. These differences were statistically significant (p < 0.05). Particularly, the LDL/HDL ratio was markedly higher in the hypertensive group compared to the normotensive and prehypertensive groups. This difference was

also statistically significant (p = 6.56e-07) (Table 3).

Analysis of lipoprotein profiles revealed that lipoprotein (a) levels were significantly higher in the hypertensive group compared to normotensive and prehypertensive groups, with values averaging(26.69±14.99)mg/dL. Similarly, the ApoB/ApoA ratio was substantially greater in the hypertensive group (1.30 ± 0.30), and correlating with increased blood pressure categories. These findings were statistically significant, with the ApoB/ApoA ratio showing a particularly strong association(F=17.59 , p=6.47^{e-07}), (Table 3).

6. Discussion

In this investigation, the prevalence of hypertension within the cohort was marginally below the 8.8% standardized rate for 12 to 17-year-old Chinese adolescents documented in 2018[8], possibly reflecting the limited sample size. Nevertheless, the considerable identification of 32.9% of the children as prehypertensive warrants attention. Studies indicate an approximate 7% annual transition rate from prehypertension to hypertension, marking a significant risk for the onset of hypertension in youth[15]. This represents a formidable challenge for health systems. Detected lipid irregularities in prehypertensive children emphasize the importance of lipid profile monitoring and lifestyle interventions to lessen the risk of hypertension and cardiovascular disease (CVD).

Epidemiological research has affirmed the association between serum cholesterol, blood pressure, and the risk of CVD[15,16]. The higher cholesterol levels found in hypertensive and prehypertensive participants of this study are consistent with these findings and signal an increased risk of atherosclerosis and subsequent CVD starting from a young age.

The link between serum total cholesterol and CVD risk is well established, with shifts in cholesterol levels due to pharmacological or lifestyle changes mirroring fluctuations in CVD incidence[17]. This evidence has led to the recognition of plasma total cholesterol as a predictive marker for CVD[16,18].

While triglycerides increased to a lesser extent than other lipid markers, our study noted significantly elevated levels among the hypertensive group, a difference that was statistically significant (p=1.09^{e-03}). Certain studies have pointed to a stronger correlation between hypertriglyceridemia, body fat distribution, and saturated fat-rich diets than with changes in blood pressure[19,20]. This study did not evaluate fat distribution or dietary patterns. The role of elevated triglyceride levels as an independent prognostic factor for CVD is still contested.

Lower HDL levels were observed in children with hypertension and prehypertension, which literature indicates may raise the risk of CVD. Higher HDL levels are deemed protective against hypertension. Historical research suggests that higher HDL concentrations are associated with a lower likelihood of CVD, with a 1 mg/dL increase in HDL potentially reducing coronary artery risk by 2-3%[16,21].

Our findings concur with prior research showing a clear connection between HT and raised LDL levels, as well as the direct correlation of high LDL with increased CVD risk. Elevated LDL and LDL/HDL ratios in hypertensive and prehypertensive subjects suggest a progressive condition commencing from youth, leading to elevated CVD risk in adulthood[22]. Therefore, these children necessitate enhanced medical care to address both blood pressure and lipid imbalances.

The interrelation of high total cholesterol, LDL levels, and the cholesterol/HDL ratio with the rising incidence of hypertension and CVD has been independently validated. Our study supports these associations, indicating a higher risk of CVD in prehypertensive and hypertensive children and underscoring the need for specialized counseling, ongoing monitoring, and follow-up[23,24].

Higher Lp(a) levels were also noted in children with hypertension and prehypertension. Although not directly linked to pediatric HT, various studies have shown that elevated Lp(a) is associated with

increased thrombotic capacity and constitutes an independent CVD risk factor, even when cholesterol and triglyceride levels are within normal ranges[25]. Lp(a) levels typically remain constant throughout life, mirroring childhood concentrations. Children with familial cardiovascular risk factors tend to have higher Lp(a) levels, highlighting the usefulness of this marker, particularly in those with adverse lipid profiles[25].

Additionally, lower ApoA1 and higher ApoB levels in hypertensive and prehypertensive children may predict early adulthood carotid intima-media thickening, thereby relating to cardiovascular risk. The ApoB/ApoA ratio accurately reflects the balance between atherogenic and anti-atherogenic lipoproteins[26,27]. In the subjects of this study with hypertension and prehypertension, the balance is skewed towards atherogenic lipoproteins, suggesting a greater CVD risk.

Rising levels of ApoB and the ApoB/ApoA1 ratio, coupled with decreased ApoA1, have been shown to predict cardiovascular events more accurately than other known risk factors, including high LDL levels[27-29]. Recent prospective studies have drawn correlations between ApoA1 and ApoB plasma levels and coronary artery disease, particularly in adults[29], indicating that the ApoB/ApoA ratio is a potent predictor. Yet, research in this area among adolescents is lacking. Our results are in line with findings by Cuban researchers such as Merlin Gar íLlanes[30] and are supported by studies from Venezuela[31] and Spain[32], indicating that children in our hypertensive cohort are at considerable risk for developing CVD.

In summary, the most pivotal biochemical markers associated with HT in our prehypertensive and hypertensive pediatric participants were elevated LDL levels, the LDL/HDL ratio, the ApoB/ApoA ratio, and high lipoprotein (a) concentrations. The prevalence of hypertension among Chinese adolescents calls for vigilant monitoring and proactive management by public health professionals.

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