The Association of Obesity with Non-Dipping Status and Laboratory Biomarkers in Hypertensive Children

Hipertansif Çocuk Hastalarda Obezite ve Gece Düşüşünün Olmaması Durumu Ile Laboratuvar Belirteçlerinin Ilişkisi

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ABSTRACT

Objective: To investigate the 24-h ambulatory blood pressure monitoring (ABPM) and laboratory markers associated with target organ damage and to evaluate the relationship between obesity and non-dipping status on ABPM in children with essential hypertension (HT).
Methods: We conducted a study using a database of patients aged 5-18 years. Inclusion criteria were: subjects where records documented a blood pressure >95th percentile for age, sex, and height by a referring physician had ABPM for diagnosis. The data of target organ damage, body mass index (BMI), and laboratory parameters were collected.
Results: This study included 175 patients (48 lean, 127 overweight+obese). Thirty-seven patients had white coat hypertension (WCH), 29 patients had Pre-HT, and 109 patients had HT. There were no significant differences in mean age, gender or mean BMI of children between the groups (p>0.05). Non-dipper status and uric acid level were significantly higher in overweight+obese patients compared to normal weight patients (55.9% vs. 39.5%, p=0.04, 4.9±1.4 vs. 5.3±1.3, p=0.03). Nine patients had left ventricular hypertrophy (2 WCH, 7 HT) and 17 patients had retinopathy (4 WCH, 2 Pre-HT, 11 HT).
Discussion: Obese patients should be screened for HT by ABPM. WCH and Pre-HT are also not innocent and cause significant morbidity.

Keywords: ambulatory blood pressure monitoring, white coat hypertension, dipping status, prehypertension

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ÖZET

Amaç: Esansiyel hipertansiyonu (HT) olan çocuklarda 24 saatlik ambulatuar kan basıncı monitorizasyonu (ABPM) ve laboratuar belirteçleri ile hedef organ hasarı arasındaki ilişkiyi ve obezite ile ABPM'de gece düşüşü olmaması durumu arasındaki ilişkiyi değerlendirmek amaçlanmıştır.
Yöntem: 5-18 yaş arasında olan ve klinik kan basıncı ölçümü yaş, cinsiyet ve boya göre >95 persentilde olan ve ABPM ile değerlendirilien hastalar çalışmaya alınmıştır. Hedef organ hasarı verileri, vücut kitle indeksi (VKİ) ve laboratuar parametreleri verileri dosya kayıtları taranarak elde edilmiştir.
Bulgular: Bu çalışmaya 175 hasta (48 normal kilolu, 127 fazla kilolu+obez) dahil edilmiştir. Otuz yedi hasta beyaz önlük hipertansiyonu (BÖH), 29 hasta prehipertansiyon (Pre-HT) ve 109 hasta HT grubunda yer almıştır. Gruplar arasında yaş, cinsiyet ve ortalama VKİ açısından fark saptanmadı (p>0.05). Ürik asit düzeyi ve gece düşüşü olmaması fazla kilolu+obez olan hasta grubunda anlamlı olarak yüksek saptandı (4.9±1.4 vs. 5.3±1.3, p=0.03, %55.9 vs. %35.9, p=0.04). Dokuz hastada sol ventrikül hipertrofisi (2 BÖH, 7 HT) ve 17 hastada retinopati (4 BÖH, 2 Pre-HT, 11 HT) saptandı.
Sonuç: Obez hastalar HT açısından ABPM ile taranmalıdır. Pre-HT ve BÖH da kardiyovasküler morbidite açısından HT gibi masum olmayan riskli bir durumdur.

Anahtar Sözcükler: Ambulatuar kan basıncı monitorizasyonu, beyaz önlük hipertansiyonu, gece düşüşü, prehipertansiyon

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INTRODUCTION

The prevalence of hypertension (HT) shows a constant increase in children and adolescents in favor of primary HT. Obesity is the main inducer for the increment in the prevalence of HT in childhood as in adults (1, 2). Hypertension is a leading risk factor for cardiovascular disease and mortality (3). Epidemiological studies have shown a strong relationship between obesity and cardiovascular diseases (4).

The mechanism of HT in obesity seems to be multifactorial, with hyperinsulinemia, hyperlipidemia, renal structural deformation, and endothelial dysfunction comprising major components of this mechanism. Although the relationship between hypertension and uric acid has been known for about half a century, this issue has been explained more detail recently. The association between uric acid and HT is confounded by numerous factors. For instance, elevated serum uric acid is also observed in obese subjects which in turn affects the development of HT (5-7).

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) has been immensely helpful in diagnosing hypertension in children, allowing physicians to identify white coat hypertension (WCH), masked HT, and evaluate nocturnal dipping status. In adults, obesity is associated with nocturnal HT and abnormal dipping status on 24-hour ABPM. Nocturnal HT and abnormal dipping status have been shown to significantly affect prognosis and target organ damage in adults and children (8).

The aim of this study is to investigate the ABPM and laboratory markers associated with target organ damage and to evaluate the relationship between obesity and non-dipping status on ABPM in children with essential HT which may eventually lead to better treatments and prevention methods.

METHODS

We conducted a cross-sectional study using a database of patients aged 5-18 years who had undergone a first time 24-hour ABPM at Gazi University Faculty of Medicine Pediatric Nephrology Outpatient Clinic between January 2008 and January 2013. The data was collected retrospectively. Inclusion criteria were: subjects where records documented a BP >95th percentile for age, sex, and height by a referring physician on at least three separate occasions and were in turn confirmed in pediatric nephrology clinic by auscultation and had ABPM for initial diagnostic assessment. Patients who receiving antihypertensive, glucocorticoid, immunosuppressant, and stimulant treatment before or during the ABPM and who had any kidney, cardiac or neurological disorders were excluded.

Office BP measurements

The clinical BP measurement values were collected from hospital records. The routine procedure for BP measurement in our clinic is to measure in a quiet, non-crowded room. After five- minute resting, BP is measured in the appropriate position as the cubital fossa would remain at the heart level. The length of the inflated part of the cuff is approximately 40% of the distance between the acromion and the olecranon. The stethoscope is placed on the brachial artery at the lower edge of the sleeve. The systolic BP is measured when the first Korotkoff sound was heard and diastolic BP is measured when the Korotkoff sound was disappeared (5th Korotkoff sound). The mean of the measurements which are usually repeated 3 times were recorded as the office BP. SBP and DBP percentiles were calculated according to the normograms recommended by the National High Blood Pressure in Children and Adolescents institute. HT was defined in a child or adolescent if the mean SBP or DBP was above the 95th percentile for gender, age and height on three or more occasions. For adolescents aged 16 or older, the definition of HT was based on the absolute cutoff used for adults as high-normal (130-139/85-89 mmHg) and HT (≥140/90 mmHg) (9).

ABPM

All ABPMs were performed using Spacelabs Monitor model 90207 (Spacelabs Medical, Redmond, WA). The monitor was placed by nursing staff in our office at the time of clinic visit. Appropriate cuff size was determined using guidelines from the report on diagnosis, evaluation, and treatment of pediatric HT . Readings were taken every 20 minutes while awake and every 60 minutes while asleep. Patients were asked to keep a diary showing sleep and wake times. At least 40 readings were considered satisfactory for analysis.

The data were analyzed by calculating 24-h mean SBP and DBP, daytime SBP and DBP, nighttime SBP and DBP as described in the American Heart Association (AHA) statements on ABP. Elevated BP load was defined as more than 25% of recordings of SBP or DBP measurements being ≥95th percentile for gender and height respectively. In addition, the patients were classified as dippers if the mean SBP and/or DBP decreased by ≥10% during the sleep period, and this was calculated as follows: (mean daytime-mean nighttime/mean daytime) x100. Subjects with a nighttime drop of SBP or DBP of <10% of daytime values were considered to be non-dippers (10).

Based on the recommendations of the AHA statement patients were classified into three groups: WCH, prehypertension (pre-HT) and HT. WCH was defined as office BP percentiles of >95th percentile, 24-h mean SBP of <95th percentile and SBP load of <25%; Pre-HT was defined as mean ambulatory BP less than the 95th percentile, but with a BP load of ≥25%. Ambulatory HT was defined as office BP of >95th percentile, 24-h mean SBP of >95th percentile and SBP load of >25% (10, 11).

Anthropometric measurements

As part of routine clinical care, height was measured with a stadiometer and weight was measured on a calibrated scale with the child wearing light clothing. Kilogram (kg) / height^2 (m^2) formula was used to calculate body mass index (BMI). After evaluating the BMI percentiles for the Turkish population based on age and gender, subjects were grouped into categories based on body mass index (BMI) as: lean and overweight+obese (lean:15th-85th BMI percentile, overweight: >85th-95th percentile and obese ≥95th percentile) (12).

Additionally, the data of target organ damage (echocardiography, ophthalmologic examination), and laboratory parameters were collected by querying our database. Blood samples were obtained from all study subjects after a 12-h fasting period. The data of complete blood count, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting lipid profile (cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) were collected.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) version 15 was used. Chi-Square (x^2) test and Fisher exact test were used for statistical evaluation of categorical variables. The quantitative variables in which the parametric test conditions were achieved were evaluated by student T test in the comparison of the two groups and one-way analysis of variance by more than two groups. Mann-Whitney U test was used for the two groups and Kruskal Wallis H test was used for the comparison of more than two groups. In the one-way analysis of variance, Tukey and Kruskal Wallis variance analysis were used as multiple comparison tests and the Mann-Whitney U test with Bonferroni correction was used. In all statistical analyzes, $p<0.05$ was accepted as the significance level.

Ethical statement

The study adhered to the principles of the Declaration of Helsinki and was approved by the local Ethics Committee (Date: 27 April 2013; Protocol Number: 213).

RESULTS

This retrospective study included 175 patients who were evaluated for HT. According to ABPM measurements, 37 patients had WCH, 29 patients had Pre-HT, and 109 patients had HT. There were no differences in mean age, gender or mean BMI of children between the groups. The comparative demographic, clinical, laboratory and ABPM parameters among 3 groups of patients are given in Table 1.

Table 1. Demographic, clinical, hemogram and biochemical characteristics of study population.

	WCH (n=37)	Pre-HT (n=29)	HT (n=109)	p
Age, years	13.9±2.1	14.0±2.2	13.8±2.5	0.788
Male, n (%)	23 (62.1)	18(62)	70(64.2)	0.954
BMI, kg/m^2	27.9±5.4	28.8±5.0	28.7±6.6	0.789
LVH, n (%)	2 (5.4%)	-	7 (6.4%)	
Retinopathy, n (%)	4 (10.8%)	2 (6.8%)	11 (10%)	
Uric acid, mg/dL	4.9±1.6	5.3±1.3	5.1±1.4	0.841
Hb (g/dL)	14.1±1.4	13.7±1.3	14.0±1.3	0.338
WBC (x10^3/mm^3)	7.7±1.9	7.6±1.7	8.0±2.1	0.892
Plt (x10^3/mm^3)	277.1±70.1	314.4±70.0	292.2±63.2	**0.033**[a]
AST (IU/l)	21.4±8.3	23.6±9.5	24.4±12.9	0.334
ALT (IU/l)	23.5±17.4	24.4±14.5	26.1±25.4	0.621
Total Cholesterol, mg/dL	155.1±19.3	163.2±30.4	162.2±28.7	0.169
Triglycerides, mg/dL	113.8±73.4	100.1±39.0	120.6±70.1	0.581
HDL Cholesterol, mg/dL	45.6±9.6	44.8±10.6	44.7±11.5	0.952
LDL Cholesterol, mg/dL	85.3±18.6	101.0±26.2	95.1±21.0	**0.042**[a]
VLDL Cholesterol, mg/dL	20.6±8.4	21.1±8.1	25.9±14.2	0.217

Abbreviations: BMI, body mass index; LVH, left ventricular hypertrophy; Hb, hemoglobine; WBC, White blood cell; Plt, platelet; AST, aspartate transaminase; ALT, alanine transaminase; LDL, low-density lipoprotein; VLDL,very low-density lipoprotein; HDL, high-density lipoprotein
[a] All groups vs. each group

Table 2. ABPM findings in WCH, Pre-HT and HT groups

ABPM parameters	WCH	Pre-HT	HT	p
24-hour BP, mmHg	73.9±4.8	77.0±5.1	81.5±8.8	**<0.001**[a]
24-hour SBP, mmHg	113.1±6.2	119.8±5.0	125.3±10.5	**<0.001**[a]
24-hour DBP, mmHg	61.9±4.3	65.6±4.6	69.7±8.5	**<0.001**[a]
Daytime SBP, mmHg	118.5±7.1	125.1±6.6	130.1±11.1	**<0.001**[b]
Daytime DBP, mmHg	67.3±4.4	70.9±5.6	74.1±9.3	**<0.001**[b]
Nighttime SBP, mmHg	105.8±6.2	112.4±6.1	117.0±14.9	**<0.001**[a]
Nighttime DBP, mmHg	56.1±4.5	58.6±5.1	63.1±7.8	**<0.001**[c]
Daytime SBP load (%)	11.6±9.1	29.4±13.9	45.2±24.8	**<0.001**[a]
Nighttime SBP load (%)	13.6±10.1	34.5±16.0	50.2±27.7	**<0.001**[a]
Daytime DBP load (%)	10.6±7.4	22.1±14.9	32.1±21.2	**<0.001**[b]
Nigtttime DBP load (%)	14.8±11.6	28.4±15.5	38.9±26.5	**<0.001**[b]
Non-dipper status, n (%)	17 (19.1)	11 (12.3)	61 (68.5)	0.128

Abbreviations: BP, blood pressure, SBP, systolic blood pressure; DBP, diastolic blood pressure
[a]All groups vs. each group, [b]WCH vs. Pre-HT and HT, [c]HT vs WCH and Pre-HT

Table 3. Demographic, clinical, hemogram and biochemical characteristics of normal weight and overwieght+obese patients

	Normal weight (n=48)	Overweight+Obese (n=127)	P
Age, years	14.3±3.4	14.7±2.5	0.3
Male n (%)	32 (66.6)	79 (62.2)	0.2
LVH n (%)	3 (6.2)	6 (4.7)	-
Retinopathy n (%)	5 (10.4)	12 (9.4)	0.05
Uric acid, mg/dL	4.9±1.4	5.3±1.3	**0.03**
Hb (g/dL)	14.3±1.4	14.1±1.2	0.05
WBC (x10^3/mm^3)	7.8±2.8	8.1±2.6	0.2
Plt (x10^3/mm^3)	261.5±65	304.2±63.7	**<0.001**
AST (IU/l)	21.7±10.8	24.5±11.5	**0.02**
ALT (IU/l)	20.3±23.8	27.3±21.4	**<0.001**
Total Cholesterol, mg/dL	151.8±25.7	163.8±27.1	**0.005**
Triglycerides, mg/dL	90.4±37.6	125.1±72.8	**0.001**
HDL Cholesterol, mg/dL	49.9±15.7	44.8±9.7	**0.02**
LDL Cholesterol, mg/dL	89.4±23.8	96.1±21.6	0.1
VLDL Cholesterol, mg/dL	18.3±8.4	24.2±12.4	0.09

Abbreviations: LVH, left ventricular hypertrophy; Hb, hemoglobine; WBC, White blood cell; Plt, platelet; AST, aspartate transaminase; ALT, alanine transaminase; LDL, low-density lipoprotein; VLDL,very low-density lipoprotein; HDL, high-density lipoprotein

Table 4. ABPM findings in normal weight and overwieght+obese patients

ABPM parameters	Normal weight (n=48)	Overweight+Obese (n=127)	p
24-hour BP, mmHg	76.3±5.6	78.7±7.2	**<0.001**
24-hour SBP, mmHg	122.1±8.2	123.4±8.5	0.06
24-hour DBP, mmHg	69.7±4.9	68.2±7.5	**<0.001**
Daytime SBP, mmHg	129.7±6.1	130.2±10.2	0.1
Daytime DBP, mmHg	74.6±5.1	70.6±7.3	**<0.001**
Nighttime SBP, mmHg	113.7±6.6	118.1±9.9	**<0.001**
Nighttime DBP, mmHg	59.6±5.7	60.6±7.1	0.07
Daytime SBP load (%)	15.1±7.3	12.3±6.9	**<0.001**
Nighttime SBP load (%)	24.7±6.9	20.6±9.3	**<0.001**
Daytime DBP load (%)	15.8±10	32.8±16.3	**<0.001**
Nigtttime DBP load (%)	10.5±8	27.7±19.8	**<0.001**
Non-dipper status, n (%)	19 (39.5)	71 (55.9)	**0.04**

Abbreviations: BP, blood pressure, SBP, systolic blood pressure; DBP, diastolic blood pressure

According to BMI percentile categories, there were 48 lean patients and 127 overweight+obese patients. Mean 24-hour, daytime and nighttime systolic and diastolic BPs and dipping status are shown in Table 2 and 4. Non-dipping status was not significantly different between HT, Pre-HT and WCH groups. Of the 48 subjects in normal weight group, 19 were classified as non-dippers (39.5%). Of the 127 subjects in the obese+overweight group, 71 were classified as non-dippers (55.9%). Non-dipper status was significantly higher in overweight + obese patients compared to normal weight patients (p=0.04). Uric acid, platelet, AST, ALT, cholesterol, triglyceride, and HDL levels were significantly higher in overweight + obese patients compared to normal weight patients (Table 3).

There was a positive correlation between UA level and 24-h SBP (r=0.29, p<0.001), daytime SBP (r=0.233, p<0.001), and nighttime SBP (r=0.282, p<0.001). Total cholesterol levels were positively correlated with 24-h SBP load (r=0.115, p<0.05), 24-h DBP load (r=0.187, p<0.05) and daytime DBP (r=0.203, p<0.05). A positive correlation was observed between VLDL levels and 24-h SBP (r=0.212, p<0.05), 24-h DBP (r=0.252, p<0.05), nighttime DBP (r=0.273, p<0.001), 24-h DBP load (r=0.315, p<0.001) and nighttime DBP load (r=0.313, p<0.001).

DISCUSSION

In this study, the patients referred for evaluation of suspected hypertension, obesity was significantly associated with non-dipping status. Overweight and obese children with HT were also found to have higher serum uric acid levels compared to normal weight children with HT.

A relationship between non-dipper status and cerebrovascular diseases was shown previously. The prevalence of non-dipping status increases with obesity in adults (13). In obese children, it is also reported that there is a change in circadian BP rhythm and an increase in non-dipper status (14). It is thought that the decrease of night fall in obese patients may be an early sign of changes in BP regulation and development of target organ damage (15). There are few available data on the prevalence of non-dipping status in the general pediatric population. Framme et al. found that pediatric obesity only had a significant effect on nocturnal dipping in females of a total of 80 subjects (25 in the lean group and 55 in the obese group) (15), whereas Macumber et al. found an association between pediatric obesity and non-dipping status in both genders as in our study (8).

In children and adolescents, the increase in the prevalence of hypertension is highly associated with obesity as the risk of HT is 3.5-fold higher in obese children (16, 17). In many studies, even normotensive obese patients were found to have significantly higher blood pressure but in normal limits (6, 16). A population-based study in which individuals were accessed by house visits throught Turkey (3622 children, 5-18 years) revealed the prevalence of overweight, obesity and HT as 9.3, 8.9 and 6.1% and obese children had the highest rate of HT (11.4% vs. 5.6%) (17). Thus, the most important risk factor for the development of essential HT likely seems to be the presence of obesity.

In our study, we have found that one fourth of hypertensive patients have WCH. In childhood, WCH is more common compared to adults (18). In a study conducted on 90 patients diagnosed with HT by clinical BP measurement method, it was detected that 28% of children had WCH. To rule out WCH, ABPM is generally recommended (19). White coat hypertension is considered as a pre-hypertensive condition and was associated with risk of developing HT and target organ damage in adulthood (20, 21). In the studies employing data for children, it was shown that WCH was associated with increased left ventricular mass index and impaired arterial elasticity (22, 23). In our study, we demonstrated that target organ damage (2 patients with left ventricular hypertrophy (LVH), 4 patients with retinopathy) were also observed among patients with WCH.

Previous studies have shown that uric acid elevation is strongly associated with HT and obesity in children and adolescents. Elevated uric acid levels have been reported that there is a 1.6-2-fold increase for development of HT (24). Each 1 mg/dl increase in uric acid levels was shown to increase the risk of Pre-HT and HT by at least 50% (25). A significant relationship between SBP-DBP and uric acid levels was also detected in a large cohort of children evaluated with ABPM (26). High levels of serum uric acid were observed in about 90% of adolescents with recent onset hypertension and the serum uric acid levels correlated with BP values (27). In another study indicated that a positive association between uric acid, and office, daytime and night-time SBP, insulin and triglycerides (28). Akcaboy et al. studied the effect of plasma NO_x levels on cardiac function in hypertensive pediatric patients and reported a significant positive correlation between ABPM values and uric acid levels and a negative correlation between plasma NO_x levels and uric acid, BMI, triglyceride and VLDL values (29). In our study, overweight-obese children were found to have higher serum uric acid levels compared to normal weight hypertensive children and uric acid level was positively correlated with ABPM values.

Blood viscosity is determined by four different parameters. They are hematocrit, erythrocyte deformability, erythrocyte aggregation and plasma viscosity (30, 31). Hypertension, obesity, high serum LDL cholesterol levels, and low serum HDL cholesterol levels, as well as other cardiovascular disease risk factors have been found to be associated with an increase in blood viscosity (32, 33). Platelet aggregation and blood viscosity are increased in hypertensive patients regardless of BMI. In normotensive obese patients, there is a risk for platelet aggregation and increased viscosity which is correlated with the BMI values. This finding suggests that despite of normal BP measurements in obese patients, an essential need for careful follow-up for development of HT and endothelial dysfunction should be performed. Obese children have been shown to have higher total cholesterol and triglyceride levels have a higher prevalence of dyslipidemia and HT (34, 35). In our study, LDL and platelet levels were found to be significantly higher in the Pre-HT group than in the WCH group. Moreover overweight + obese patients were shown to have higher UA, Hb, Plt, total cholesterol, triglyceride and lower HDL compared to patients with normal weight.

Although LVH (9 patients) and retinopathy (17 patients) were found in very few patients in our study, still we can emphasize the importance of delayed detection of HT in terms of the development of target organ damage as the patients were included in the study at their first presentation.

CONCLUSION

Our findings revealed that overweight and obesity play an important role in the development of childhood HT. Since HT is an important complication of obesity, it has been shown that obese patients should be screened for HT by ABPM. Demonstration of target organ damage in WCH, Pre-HT and HT groups supported the fact that WCH and Pre-HT are also not innocent and cause significant morbidity and mortality for cardiovascular diseases as HT.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1.Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA. 2006;295(13):1549-55.

2.Crawford D. Population strategies to prevent obesity. BMJ. 2002;325(7367):728-9.

3.Falkner B. Hypertension in children and adolescents: epidemiology and natural history. Pediatr Nephrol. 2010;25(7):1219-24.

4.Sundell J. Obesity and diabetes as risk factors for coronary artery disease: from the epidemiological aspect to the initial vascular mechanisms. Diabetes Obes Metab. 2005;7(1):9-20.

5.Tian S, Liu Y, Xu Y, Feng A. Does obesity modify the epidemiological association between hyperuricemia and the prevalence of hypertension among Northern Chinese community-dwelling people? A Chinese population-based study. BMJ Open. 2019;9(11):e031803.

6.Kotsis V, Stabouli S, Papakatsika S, Rizos Z, Parati G. Mechanisms of obesity-induced hypertension. Hypertens Res. 2010;33(5):386-93.

7.Breckenridge A. Hypertension and hyperuricaemia. Lancet. 1966;1(7427):15-8.

8.Macumber IR, Weiss NS, Halbach SM, Hanevold CD, Flynn JT. The Association of Pediatric Obesity With Nocturnal Non-Dipping on 24-Hour Ambulatory Blood Pressure Monitoring. Am J Hypertens. 2016;29(5):647-52.

9.Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016;34(10):1887-920.

10. Flynn JT, Daniels SR, Hayman LL, Maahs DM, McCrindle BW, Mitsnefes M, et al. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. Hypertension. 2014;63(5):1116-35.

11. Urbina E, Alpert B, Flynn J, Hayman L, Harshfield GA, Jacobson M, et al. Ambulatory blood pressure monitoring in children and adolescents: recommendations for standard assessment: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee of the council on cardiovascular disease in the young and the council for high blood pressure research. Hypertension. 2008;52(3):433-51.

12. Barlow SE, Dietz WH. Obesity evaluation and treatment: Expert Committee recommendations. The Maternal and Child Health Bureau, Health Resources and Services Administration and the Department of Health and Human Services. Pediatrics. 1998;102(3):E29.

13. Kotsis V, Stabouli S, Bouldin M, Low A, Toumanidis S, Zakopoulos N. Impact of obesity on 24-hour ambulatory blood pressure and hypertension. Hypertension. 2005;45(4):602-7.

14. Marcovecchio ML, Patricelli L, Zito M, Capanna R, Ciampani M, Chiarelli F, et al. Ambulatory blood pressure monitoring in obese children: role of insulin resistance. J Hypertens. 2006;24(12):2431-6.

15. Framme J, Dangardt F, Marild S, Osika W, Wahrborg P, Friberg P. 24-h Systolic blood pressure and heart rate recordings in lean and obese adolescents. Clin Physiol Funct Imaging. 2006;26(4):235-9.

16. Gilardini L, Parati G, Sartorio A, Mazzilli G, Pontiggia B, Invitti C. Sympathoadrenergic and metabolic factors are involved in ambulatory blood pressure rise in childhood obesity. J Hum Hypertens. 2008;22(2):75-82.

17. Aghamohammadzadeh R, Heagerty AM. Obesity-related hypertension: epidemiology, pathophysiology, treatments, and the contribution of perivascular adipose tissue. Ann Med. 2012;44 Suppl 1:S74-84.

18. Stabouli S, Kotsis V, Toumanidis S, Papamichael C, Constantopoulos A, Zakopoulos N. White-coat and masked hypertension in children: association with target-organ damage. Pediatr Nephrol. 2005;20(8):1151-5.

19. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. Pediatrics. 2004;113(3 Pt 1):475-82.

20. Graves JW, Althaf MM. Utility of ambulatory blood pressure monitoring in children and adolescents. Pediatr Nephrol. 2006;21(11):1640-52.

21. Florianczyk T, Werner B. Usefulness of ambulatory blood pressure monitoring in diagnosis of arterial hypertension in children and adolescents. Kardiol Pol. 2008;66(1):12-7; discussion 8.

22. Litwin M, Niemirska A, Ruzicka M, Feber J. White coat hypertension in children: not rare and not benign? J Am Soc Hypertens. 2009;3(6):416-23.

23. Sorof JM. White coat hypertension in children. Blood Press Monit. 2000;5(4):197-202.

24. Feig DI. The role of uric acid in the pathogenesis of hypertension in the young. J Clin Hypertens (Greenwich). 2012;14(6):346-52.

25. Viazzi F, Antolini L, Giussani M, Brambilla P, Galbiati S, Mastriani S, et al. Serum uric acid and blood pressure in children at cardiovascular risk. Pediatrics. 2013;132(1):e93-9.

26. Jones DP, Richey PA, Alpert BS, Li R. Serum uric acid and ambulatory blood pressure in children with primary hypertension. Pediatr Res. 2008;64(5):556-61.

27. Lurbe E, Torro MI, Alvarez-Pitti J, Redon J, Borghi C, Redon P. Uric acid is linked to cardiometabolic risk factors in overweight and obese youths. J Hypertens. 2018;36(9):1840-6.

28. Orlando A, Cazzaniga E, Giussani M, Palestini P, Genovesi S. Hypertension in Children: Role of Obesity, Simple Carbohydrates, and Uric Acid. Front Public Health. 2018;6:129.

29. Akcaboy M, Kula S, Goktas T, Nazliel B, Terlemez S, Celik N, et al. Effect of plasma NOx values on cardiac function in obese hypertensive and normotensive pediatric patients. Pediatr Nephrol. 2016;31(3):473-83.

30. Kensey KR. The mechanistic relationships between hemorheological characteristics and cardiovascular disease. Curr Med Res Opin. 2003;19(7):587-96.

31. Lee AJ, Mowbray PI, Lowe GD, Rumley A, Fowkes FG, Allan PL. Blood viscosity and elevated carotid intima-media thickness in men and women: the Edinburgh Artery Study. Circulation. 1998;97(15):1467-73.

32. Rampling MW. Haemorheological disturbances in hypertension: the influence of diabetes and smoking. Clin Hemorheol Microcirc. 1999;21(3-4):183-7.

33. Bogar L. Hemorheology and hypertension: not "chicken or egg" but two chickens from similar eggs. Clin Hemorheol Microcirc. 2002;26(2):81-3.

34. Pereira A, Guedes AD, Verreschi IT, Santos RD, Martinez TL. Obesity and its association with other cardiovascular risk factors in school children in Itapetininga, Brazil. Arq Bras Cardiol. 2009;93(3):253-60.

35. Quijada Z, Paoli M, Zerpa Y, Camacho N, Cichetti R, Villarroel V, et al. The triglyceride/HDL-cholesterol ratio as a marker of cardiovascular risk in obese children; association with traditional and emergent risk factors. Pediatr Diabetes. 2008;9(5):464-71.