Original Article / Özgün Araştırma

The Level of Serum Uric Acid as Evidence of Endothelial Dysfunction in Normal Weight and Obese Children with Primary Hypertension

Hipertansiyonu Olan Normal Ağırlıklı ve Obez Çocuklarda Endotel Disfonksiyon Göstergesi Olarak Serum Ürik Asit Düzeyinin Yeri

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Abstract

Objective: Primary hypertension (HT) and obesity with a global increase in prevalence in children has become a critical health problem. HT and obesity are among the well-established cardiovascular risk factors. In this study, we investigated the relationship between arterial stiffness (AS) and serum uric acid (UA) levels in normal-weight and obese children with primary HT.

Materials and Methods: This prospective study was conducted at the university hospital between September 2016 and September 2017. The children aged 6-18 years and recently diagnosed with HT (n=77) were categorized into two groups based on body mass index values as group 1 (HT + obese) (n=46) and group 2 (HT + normal weight) (n=31). The control group (n=35) consisted of age and gender-matched healthy children. The AS of all children included in the study was measured by ossilometric methods using mobil-O-Graph.

Results: A total of 112 children with a mean age of 13.2±3.1 years and most males (61.6%) were included in this study. The values of pulse wave velocity (PWV), central systolic blood pressure (SBP)- diastolic blood pressure (DBP), peripheral SBP-DBP, mean BP, and cardiac output in both HT groups (HT + normal weight and HT + obese) were significantly higher than those in the control group ($p<0.05$). The pulse wave reflection (%) was the lowest in the HT + obese group. When the serum UA levels were compared among the groups, the highest value was found in the HT + obese group.

Conclusions: A higher AS-PWV was detected in the normal weight and the obese children with a recent diagnosis of primary HT compared with the control group.

Öz

Amaç: Çocuklarda primer hipertansiyon (HT) ve obezite, prevalansının tüm dünyada artmasıyla birlikte kritik bir sağlık sorunu haline gelmiştir. HT ve obezite, iyi bilinen kardiyovasküler risk faktörleri arasındadır. Bu çalışmada, primer HT'si olan normal kilolu ve obez çocuklarda arteriyel sertlik (AS) ile serum ürik asit (UA) düzeyleri arasındaki ilişkiyi araştırmayı amaçladık.

Keywords
Arterial stiffness, children, hypertension, obesity

Anahtar Kelimeler
Arter sertliği, çocuklar, hipertansiyon, obezite

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Gereç ve Yöntemler: Bu prospektif çalışma Eylül 2016 ve Eylül 2017 tarihleri arasında bir üniversite hastanesinde yapıldı. Altı - on sekiz yaş arası ve yakın zamanda HT tanısı almış (n=77) çocuklar, vücut kitle indeksi değerlerine göre grup 1 (HT + obez) (n=46) ve grup 2 (HT + normal kilo) (n=31) olarak iki gruba ayrıldı. Yaş ve cinsiyet açısından aynı olan sağlıklı çocuklar kontrol grubunu (n=35) oluşturdu. Çalışmaya dahil edilen tüm çocukların arter sertliği Mobil-O-Graph kullanılarak ossilometrik yöntemlerle ölçüldü.
Bulgular: Ortalama yaşları 13,2±3,1 yıl olan ve çoğu erkek (%61,6) olan toplam 112 çocuk bu çalışmaya dahil edildi. Her iki HT grubunda (HT + normal ağırlık ve HT + obez) nabız dalga hızı (PWV), santral sistolik kan basıncı (SKB)- diyastolik kan basıncı (DKB), periferik SKB-DKB, ortalama KB ve kardiyak debi değerleri kontrol grubundan anlamlı derecede yüksekti (p<0,05). Nabız dalga yansıması (%), HT + obez grubunda en düşüktü. Gruplar arasında serum UA düzeyleri karşılaştırıldığında, en yüksek değer HT + obez grubunda bulundu.
Sonuç: Normal kilolu ve yakın zamanda primer HT tanısı alan obez çocuklarda kontrol grubuna göre daha yüksek AS-PWV saptandı.

Introduction

Primary hypertension (HT) with a global increase in prevalence in children has become a critical health problem (1-3). Obesity, which has an increasing frequency in childhood, is primarily an essential factor among the underlying causes of pediatric HT. Obesity seems to be a fundamental problem in deve loped and developing countries like Turkey (4). Several mechanisms have been proposed for the explanation of increased blood pressure (BP) in obese people (5). Along with an earlier age for childhood obesity, which has been reduced to levels of 6-7 years, the age for primary HT has also decreased to the levels of six years (6).

The measurement of arterial BP is a component of physical examination, it only provides information about the peripheral arteries. Therefore, the measurement of central aortic pressure and pulse-wave analysis by non-invasive methods like arterial stiffness (AS) have been suggested for a detailed assessment of vascular structures in childhood (7). However, those methods have not been in routine use yet but are mostly reserved for studies in high-risk patients. Moreover, the research on that subject is too limited (7). The increase in uric acid (UA), the end product of purine metabolism, is a risk factor for HT in children and adults (5). UA is known to cause HT by extreme vasoconstriction via increasing renin release and reducing endothelial nitric oxide production (5,8).

In this study, we aimed to investigate the relationship between AS and serum UA levels in normal-weight and obese children with primary HT.

Materials and Methods

This prospective study was conducted in the Department of Pediatrics, University Hospital between September 2016 and September 2017. The study, funded by the University Scientific Research Projects (#TPF-17018), was approved by the Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine (protocol no: 2016/982, date: 29.09.2016).

The power analysis, according to the study by Tokgöz et al. (3), showed that the sample size for each study group should be a minimum (min) of 24 people for an effect size of 5.3, an alpha of 5%, and a statistical power of 90%.

BP was measured by the same researcher during the outpatient visit via auscultation method using an aneroid manometer and an appropriate-sized cuff. The primary HT group consisted of the patients with BP values ≥95 percentile determined for age, gender, and height. The final BP value of a patient was estimated by using the mean value of two measurements at different times (8). The children with body mass index (BMI) ≥95 were defined as obese and the ones within the 5-84 percentile as normal weight according to the growth charts prepared for age and gender by the Center for Disease Control and Prevention (9).

The children aged 6-18 years and recently diagnosed with HT (n=77) were categorized into two groups based on BMI values as group 1 (HT + obese) (n=46) and group 2 (HT + normal weight) (n=31). The control group (n=35) consisted of age and gender-matched healthy children presented to the outpatient clinics for well-visits and whose BMI values were within 5-84 percentile and BP values were <90 percentile. The BP of children in the control group was measured twice in a 30-minute interval by the same nurse using an aneroid manometer, and the mean of two measurements was recorded as the final value. Informed consent forms were obtained from the patients and their families.

The exclusion criteria of the study included previous or secondary HT diagnosis, secondary obesity, the use of antihypertensives or any other medications for obesity, the presence of a genetic syndrome, diabetes mellitus, an and active infection in children aged ≤5 and ≥19 years. And also, children with office BP ≥95th percentile but ambulatory BP monitorization (ABPM) BP <95th percentile and BP load <25% were excluded from the study.

Ambulatory Blood Pressure Monitorization (ABPM)

The children with a recent diagnosis of primary HT had been monitored for BP in inpatient clinics. The monitorization of BP was performed for 24 hours using a Welch Allyn-24 hour ABPM (Version 12.0) on the right arm with an appropriate sized cuff in 20- and 30-minute intervals during awake and sleep times, respectively. The same pediatrician measured and evaluated the BP of each patient. The reference values were used to compare the recorded ABPM data, and the values ≥95th percentile and BP load ≥25% were accepted as HT. A load of BP was determined using the number of values that exceeded the 95th percentile for age, height, and the selected days (10).

Pulse Wave Analysis

Many studies reported that AS could accurately be evaluated using an automated oscillometric device (Mobil-O-Graph) (3). The velocity of the pulse wave is calculated by dividing the distance of the wave by the time used for that distance meter/second (m/sec) (1-3). When there is stiffness in the artery or a change in vascular tone, the pulse wave velocity (PWV) increases because of the reduction in the reflection of the produced wave (1).

The AS of all children included in the study (n=112) were measured by ossilometric methods using Mobil-O-Graph (I.E.M, Industrielle Entwicklung Medizintechnik und Vertriebsgesllschaft mbH, Stolberg, Germany). The mean value of three measurements with 15-minute intervals in the sitting position for each child was calculated. The measurements were uploaded to the computer using the I.E.M program and the Bluetooth function of the Mobil-O-Graph device. The central aorta systolic and diastolic pressures were determined. The vascular structures were evaluated by the pulse wave AIx@75, the peripheral resistance, the reflection of the pulse wave, and PWV.

The serum UA levels were measured in the Biochemistry Laboratory of university hospital using the autoanalyzer (C8000 Architect, Abbott, Abbott Park, IL, USA) and the commercial kits provided by the manufacturer.

Statistical Analysis

IBM SPSS (SPSS, Chicago, Illinois, USA) software was used for statistical analyses. Kolmogorov-Smirnov test was used to examine the normal distribution of quantitative variables. The intergroup comparison for normally distributed variables in independent groups was performed using either t-test or one-way variance analysis considering the number of groups, and descriptive statistics were shown as mean ± standard deviation. Mann-Whitney U or Kruskal-Wallis tests were used to comparing groups that did not distribute normally, and descriptive statistics were shown as median (25-75 percentile). Qualitative data were analyzed using the chi-square test, and descriptive statistics were shown as frequency (%). Spearman correlation analysis was used for the associations between variables. Statistical significance was accepted when the p-value was below 0.05.

Results

A total of 112 children with a mean age of 13.2±3.1 years [min-maximum (max): 6-18 years] and most males (61.6%) were included in this study. The number of cases with primary HT was 77, while 35 children were normotensive. The hypertensive patients were classified into two groups as HT + obese (n=46) and HT + normal weight (n=31) when the BMI value was ≥95th and 5-85 percentile, respectively. Table 1 demonstrates the demographics of participants. No statistically significant differences in gender, age, and height were found among the three groups (p>0.05). The weight and BMI values were the highest in the HT + obese group, as expected. The diagnostic SBP and diastolic BP (DBP) measurements in the children with primary HT were statistically significantly higher than those in the control group.

Especially for ABPM evaluation, the nocturnal SBP/DBP load was found to be relatively high in two hypertensive groups. However, no significant difference in ABPM values was found between the two HT groups (p>0.05).

The values of PWV, central SBP-DBP, peripheral SBP-DBP, mean blood pressure and cardiac output in both HT groups (HT + normal weight and HT + obese) were significantly higher than those in the control group (p<0.05). The pulse wave reflection (%) was the lowest in the HT + obese group (p=0.03) (Table 2).

The median AS-PWV value of participants was 4.8 m/sec (25^{th}-75^{th} percentile: 4.4-5.1). Logistic regression analysis revealed that the PWV value increased (>4.8 m/sec) 9.7, 2.6, and 1.2 times by the presence of HT, female gender, and advanced age, respectively (Table 3).

In hypertensive children, the AS-PWV value showed positive correlations with daytime load of SBP (r=0.287, p=0.011), daytime load of DBP (r=0.239, p=0.036), nocturnal load of SBP (r=0.233, p=0.041) and nocturnal load of DBP (r=0.343, p=0.002).

When the serum UA levels were compared among groups, the highest value was found in the HT + obese group (p<0.001, Figure 1). The serum UA levels in HT + obese, HT + normal weight, and the control groups were 6±1.1, 4.8±1.2, and 4.5±1.1 mg/dL, respectively.

Moreover, the serum UA levels in hypertensive children (n=77) showed positive correlations with PWV (r=0.233, p=0.042) and cardiac output (r=0.455, p=0.001) and negative correlations with (AIx@75) (r=-0.349, p=0.002), augmentation pressure (r=-0.284, p=0.012), and reflection magnitude (r=-0.254, p=0.026). Besides, the serum UA levels in hypertensive children had positive correlations with daily SBP (r=0.351, p=0.002), nocturnal SBP (r=0.315, p=0.005), nocturnal DBP (r=0.257, p=0.024) and nocturnal load of SBP (r=0.275, p=0.016).

Discussion

In this study, the AS-PWV measurements in normal weight and obese children with a recent diagnosis of primary HT were found significantly higher than those in the control group. Additionally, serum UA level, which is a critical indicator for endothelial damage, was the highest in the HT + obese group. Moreover, serum UA levels had shown positive correlations with nocturnal load of SBP and DBP of ABPM.

In our study, which evaluated 77 children aged between 6 and 18 years and with a recent diagnosis of primary HT, the rates of obesity and normal weight

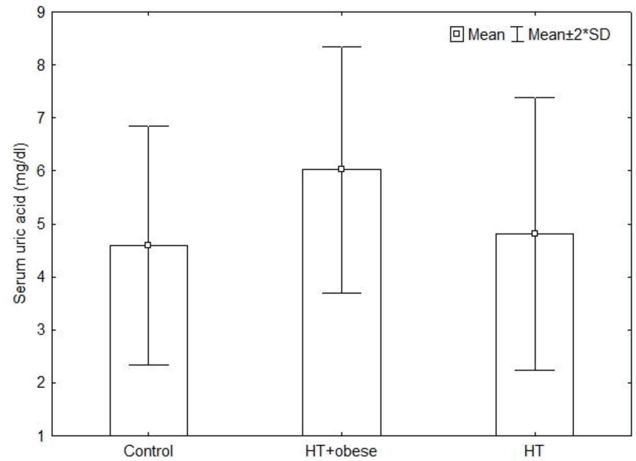

Figure 1. Comparison of serum uric acid levels for three groups
HT: Hypertension, SD: Standard deviation

Table 1. The demographic data of the patients and control group

Variables	HT + Normal weight (n= 31)	HT + Obese (n=46)	Control (n=35)	p-value
Age (year)	14 (10-16)	14 (12-16)	14 (11-15)	0.777
Gender (male/female) (n) (%)	20/11 (65/35)	29/17 (63/37)	20/15 (57/43)	0.800
Height (cm)	164 (157-172)	166 (146-174)	160 (149-170)	0.403
Height SDS	0.57 [(-)0.29-1.19]	0.42 [(-)0.37-1.26]	0.21 [(-)0.69-0.87]	0.156
Body weight (kg)	63 (43.5-71.5)	89 (75.1-103.2)	51,5 (40-64)	<0.001*
Body weight SDS	0.76 (0.3-1.28)	3.07 (2.22-3.76)	-0.04 [(-)0.8-1.07]	<0.001*
BMI (kg/m²)	22.3 (19.7-24.5)	30.8 (28.9-36.6)	20 (17.6-22.9)	<0.001*
BMI SDS	0.66 (0.03-1.07)	2.64 (2.22-3.23)	0.03 [(-)0.63-0.76]	<0.001*
Office auscultatory systolic BP (mmHg)	130 (125-135)	135 (130-140)	110 (100-115)	<0.001**
Office auscultatory diastolic BP (mmHg)	70 (65-80)	75 (70-80)	65 (60-70)	<0.001**

Data are mean ± SD or median (25-75 persantile)
HT: Hypertension, BMI: Body mass index, BP: Blood pressure, SDS: Standard deviation score
*HT + Obese versus HT + Normal weight and control
**Control versus HT + Normal weight and HT + obese

were 59.7% and 40.3%, respectively. In line with the literature, we observed that obesity has an essential role in children with HT.

In our study, both HT groups (normal weight and obese) had oscillometric ABPM. We observed that especially the nocturnal SBP and DBP loads were approximately 33-50% without any significant difference between the two HT groups. Conclusively, a critical nocturnal BP load and end-organ damage risk were demonstrated in both the normal weight and obese groups. In ABPM, the expected reduction in nocturnal BP had not been observed in 50% of the children with obesity (11). Supporting the literature, our study did not show any nocturnal reduction in BP in both HT groups. Thus, we suspect that the risk for end-organ damage would be relatively higher in those recently diagnosed patients in case of an uncontrolled BP.

Studies have found that the main determinant of primary HT is obesity. A significant relationship was determined between increased BMI and the increase in the prevalence of HT, and essential HT was detected in approximately 30% of children with obesity (10). In a study from our country, the prevalence of obesity was estimated as 8.9%, and the prevalence of HT in obese children (11.4%) was found to be approximately twice more than the children with normal weight (5.6%). The mean BMI of obese children in our study was 30.8 kg/m^2. Conclusively, we suspect that the increased BMI observed in obese children would contribute to chronic kidney disease in the future if weight loss in those children could not be achieved (10). Endothelial dysfunction has an important place among factors that cause atherosclerosis. Atherosclerosis usually has a childhood-onset while the related clinical problems

Table 2. The comparison of arterial stiffness among groups

Variables	HT + Normal weight (n=31)	HT + Obese (n=46)	Control (n=35)	p-value
PWV (m/s)	4.9 (4.6-5.1)	5 (4.7-5.2)	4.4 (4.2-4.7)	<0.001*
AIx@75 (%)	25.5±11.6	24±9.4	20.6±11	0.163
Peripheral SBP (mmHg)	122.6±11.5	127±13.9	108.8±10.7	<0.001*
Peripheral DBP (mmHg)	73 (65-76)	70.5 (65.7-78.2)	67 (63-69)	0.002*
MAP (mmHg)	93.6±7.4	96.1±9	84.4±7	<0.001*
Pulse	89.2±18.1	91.8±12.8	83.2±13.5	0.036**
Central SBP (mmHg)	105.4±9.6	106.7±10.4	96±9.6	<0.001*
Central DBP (mmHg)	70 (62-74)	68 (63.7-75)	65 (61-67)	0.003*
Cardiac output (lt/min)	5 (4.5-5.5)	5.5 (5-5.8)**	4.6 (4-5.3)	<0.001*
Pulse wave reflection (%)	59 (49-64)	53 (42.7-60.5)	56 (49-63)	0.03***
Augmentation Pressure (mmHg)	6 (4-8)	5 (3-7)	5 (3-7)	0.171

Data are mean ± SD or median (25-75 percentile)

HT: Hypertension; PWV: Pulse wave velocity, AIx@75: Augmentation index, BP: Blood pressure, MAP: Mean arterial pressure, SBP:Systolic blood pressure, DBP: Diastolic blood pressure

*Control versus HT + Obese and HT + Normal weight

**HT + Obese versus Control

***HT + Obese versus HT + Normal weight and control

Table 3. The logistic regression analysis of risk factors that affect the pulse wave velocity in arterial stiffness measurements (>4.8 m/s)

Dependent variable	Independent variable	OR	95% CI for OR		p-value
			Low	High	
AS PWV	Gender (Female)	2.647	1.049	6.679	0.039
	Age	1.233	1.063	1.429	0.006
	Group (HT)	9.728	3.534	26.782	0.001

AS: Arterial stiffness, PWV: Pulse wave velocity, HT: Hypertension, OR: Odds ratio, CI: Confidence interval generally appear in middle-to-older ages. Thus, the evaluation of the vascular structure is essential in childhood (10,11).

The measurement of AS is a method that aids identifying the atherosclerosis risk before any clinical symptoms and the prognosis of present atherosclerosis. The endothelial damage and atherosclerosis commonly seen in hypertensive patients are the most important causes of end-organ damage. Recently, the PWV and augmentation index have been frequently used to assess AS (12). In our study, we evaluated the AS measurements using the oscillometric method.

The PWV, which gives information about the vascular structures, is the most commonly used parameter in non-invasive AS evaluation (13). The PWV is low in elastic vessels, and the reflection wave reaches to aortic root in the diastole. In the case of AS, the PWV increases, and the reflection wave which reaches the aorta earlier combines with the forward wave and causes an increase in SBP.

The threshold value for PWV has been stated as 10 m/sec for the adults in the ESH-ESC guideline published in 2013. Also, measurements over 12 m/sec in middle-aged hypertensive patients were reported to indicate vascular dysfunction (14). Although there have been some studies on children to identify the threshold value for PWV, there is still no consensus on a typical value. In our study, the PWV values measured in both hypertensive groups (4.9 and 5 m/sec) were significantly higher than those of the control group (4.4 m/sec). Therefore, we suspect the presence of AS in the children with a recent diagnosis of HT, in terms of their being normal weight or obese, in our study. We also detected that HT, being of the female gender and having advanced age, caused the PWV value >4.8 m/sec with 9.7, 2.6, and 1.2 times more recently. Additionally, we observed that AS measurements correlated with both the ABPM measurements and the serum UA levels.

Hyperuricemia causes HT by endothelial dysfunction, mild tubulointerstitial damage, and inflammation via increasing renin and decreasing plasma nitric oxide levels. In HT evaluation of the pediatric patients, the serum UA level ≥5.5 mg/dL indicates essential HT strongly. In the obese patients, serum UA levels increase three times more than the levels in the normal-weight patients. In our study, we detected the maximum serum UA levels (6±1.1 mg/dL) in the HT + obese group. The serum UA level in the normal weight HT patients (4.8±1.2 mg/dL) was lower than those reported in the literature. We consider that physicians should pay attention to the elevation in UA levels in the obese HT children as an important parameter for end-organ damage during diagnosis. Additionally, we observed that the serum UA tested during the diagnostic studies correlated with most of the AS measurements (PWV, peripheral SBP/DBP, augmentation pressure, cardiac output) in both the normal weight and the obese HT children.

Among the limitations of our study, the most important one was the small size of the study group.

Conclusion

Conclusively, a higher AS-PWV was detected in the normal weight and the obese children with a recent diagnosis of primary HT compared to the control group in this study. Additionally, serum UA, an indicator of endothelial damage, was found to be at maximum levels in the HT + obese group. Therefore, we consider that the HT + obese patients who have both AS and endothelial damage should be attentively taken care of for the development of atherosclerosis. Therefore, more extensive studies are needed.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine (protocol no: 2016/982, date: 29.09.2016).

Informed Consent: Informed consent forms were obtained from the patients and their families.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.S.Ü., D.Y., A.A., T.Ü., Concept: D.Y., A.A., T.Ü., İ.K.Ö., Design: D.Y., Data Collection or Processing: H.S.Ü., D.Y., M.Y., Analysis or Interpretation: H.S.Ü., D.Y., M.Y., İ.K.Ö., Literature Search: H.S.Ü., D.Y., Writing: H.S.Ü., D.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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