

Ambulatory Blood Pressure Parameters in Office Normotensive Obese and Non-Obese Children: Relationship with Insulin Resistance and Atherosclerotic Markers

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Key Words

Ambulatory blood pressure monitoring · Obesity · Children · Hypertension · Atherosclerotic markers

Abstract

Objectives: To determine differences in ambulatory blood pressure (ABP) parameters between office normotensive obese and non-obese children and to evaluate correlations of ABP parameters with insulin resistance and the lipid profile. **Subjects and Methods:** Thirty-eight obese [body mass index (BMI) above the 95th percentile] and 38 non-obese children aged 9–17 years were recruited. All subjects who were normotensive during office visits and who underwent 24-hour ABP monitoring were evaluated. Insulin resistance and the lipid profile were also evaluated. **Results:** The mean daytime, night-time and 24-hour systolic blood pressure (SBP) and the daytime and 24-hour diastolic blood pressure (DBP) in normotensive obese children were significantly higher compared to the values in non-obese children ($p < 0.05$). There was no difference in the frequency of nocturnal non-dippers and nocturnal hypertension (night-time SBP at or above the 95th percentile) between the two groups ($p > 0.05$). Children with night-time SBP at or above the 95th percentile and non-dippers had higher atherosclerotic markers

than children with night-time SBP below the 95th percentile and dippers ($p < 0.05$). In logistic regression analysis, the low-density lipoprotein cholesterol (LDL-C):high-density lipoprotein cholesterol (HDL-C) ratio and night-time SBP had significantly positive associations with being obese in adolescents (OR 6.54, 95% CI 1.15–37.07, $p = 0.03$, and OR 1.1, 95% CI 1.01–1.19, $p = 0.02$, respectively). **Conclusion:** Normotensive obese children had higher ABP parameters. A high LDL-C:HDL-C ratio and night-time SBP were associated with an increased risk of being obese. High LDL-C:HDL-C ratios and total cholesterol:HDL-C levels in children and adolescents may be risk factors for night-time hypertension.

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Introduction

Obese children have an approximately 3-fold higher risk of hypertension than non-obese children [1]. Studies have shown that increased blood pressure (BP) levels during childhood strongly predict hypertension in young adulthood [2, 3]. BP values in children represent one of the most important measurable markers of the potential level of cardiovascular risk later in life [3]. Although auscultation using a mercury sphygmomanometer remains

the method of choice for the evaluation of hypertension in children, accumulating evidence suggests that ambulatory BP monitoring (ABPM) is a more accurate method for diagnosis and it is more closely associated with target organ damage [4]. BP values are substantially lower at night than during daytime activities. When the nocturnal drop in BP is less than 10% of its diurnal value, which is defined as a 'non-dipping' pattern, it deteriorates the clinical outcome of hypertension and increases the distant cardiovascular risk. ABPM is also helpful in the evaluation of non-dipping BP [5].

One of the important consequences of obesity is the development of insulin resistance (IR). This condition is associated with cardiovascular risk, diabetes, hypertension, and a shorter lifespan [6]. Hypertension is associated with abnormal lipid profiles in some obese children [7]. However, there are limited data reporting variations in BP during 24-hour monitoring and the associations of these variations with the lipid profile and IR in normotensive obese children [8]. We evaluated 24-hour ABPM in normotensive obese children and healthy age-matched controls. The aims of our study were: (a) to compare 24-hour ABPM, lipid profile, and IR between normotensive obese and non-obese healthy children, (b) to determine whether or not any changes in BP occur in normotensive obese children during 24-hour ABPM, and (c) to investigate any existing associations of these changes with IR and/or the lipid profile.

Subjects and Methods

This was a cross-sectional study including 38 obese children aged 9–17 years and 38 non-obese children (age-matched controls). Obese children were recruited among patients visiting the Pediatric Endocrinology and Metabolism Outpatient Clinic, Hospital of Celal Bayar University. This study was approved by the Scientific Ethics Committee of Celal Bayar University Medical School. Written informed consent was obtained from the parents of all children who underwent ABPM and biochemical investigation without any incentive or compensation.

Consensus guidelines define hypertension during childhood as BP that is, on 3 different visits, measured at or higher than the 95th percentile for age, sex and height [9]. Office hypertension was not found in all children included in this study according to consensus guidelines. Children with a history of premature or small for gestational age birth were excluded from this study because the addition of obesity to a low birth weight increases the risk of high BP [10]. Non-obese children were chosen from patients with upper respiratory infection who were visiting the Pediatric Outpatient Clinic. They had no complaints, excluding upper respiratory infection symptoms, and did not have any other diseases. They were offered participation in this study. ABPM was performed on the children who agreed to participate, after recovery from their ill-

ness. All obese and non-obese children included in this study had no history of hypertension, diabetes mellitus, endocrinological disorders, hereditary diseases or systemic inflammatory diseases. Children with habitual snoring and observed apnea (according to parent recall) were excluded from this study. The other exclusion criteria were past or current antihypertensive therapy. All participants included in this study were pubertal.

Anthropometric Evaluation

Weight was measured to the nearest 0.5 kg using a balance beam scale, and height was measured to the nearest 0.1 cm with a manual height board. The body mass index (BMI) was used as an index of relative weight. Comparison of weight, height and BMI among children requires the use of Z scores. Z scores for height and weight were calculated based on national growth charts [11]. The BMI Z score was calculated and the BMI percentile was evaluated for age and gender according to a Centers for Disease Control and Prevention growth chart [12].

Definitions

Obesity was defined as a BMI above the 95th age- and gender-specific percentiles [13]. The dipping percentile was calculated for both average systolic BP (SBP) and diastolic BP (DBP) with the following formula: $[(\text{daytime BP} - \text{nocturnal BP})/\text{daytime BP}] \times 100$. Each subject was categorized as a 'dipper' (decrease in average SBP and DBP $\geq 10\%$ during sleep) or a 'non-dipper' (decrease $< 10\%$) [14]. Ambulatory hypertension was diagnosed when the average ambulatory BP (ABP) for any period was at or above the 95th percentile BP on the basis of the subject's sex and height according to normative values for ABP [14].

ABP Monitoring

Validated oscillometric devices were used to measure the ABP (Delmar Reynolds Medical, Hertford, UK). The appropriate cuff, chosen from 3 different available sizes, was attached to the non-dominant arm. The frequency of automated reading was programmed at 20-min intervals from 8.00 a.m. to 12.00 p.m. and at 30-min intervals from 12.00 p.m. to 6.00 a.m. ABPM was performed during a normal weekday which included no psychosocial stress and normal recreational activities. Each recording began between 8.30 a.m. and 9.00 a.m. The accuracy and precision of the automated measurements performed in individual subjects by the oscillometric monitors were confirmed with a mercury sphygmomanometer at the beginning of the test period [9].

For data analysis, the whole 24-hour, awake (between 8.00 a.m. and 12.00 p.m.) and asleep (between 12.00 p.m. and 6.00 a.m.) periods were separately considered. Awake and asleep periods were defined according to fixed, narrow, clock time intervals, which more closely corresponded with the awake and asleep behavioral conditions in all subjects. For asleep periods, only ABPM profiles with at least 40 recordings, including at least 10 readings between 12.00 a.m. and 6.00 a.m., were accepted. The transition periods between wakefulness and sleep in the morning and evening, respectively, during which BP may undergo rapid changes with important inter-individual differences were excluded. The normative data for ABPM was from a widely accepted European cohort [14].

Biochemical Analysis

Venous blood samples were obtained after 10 h of fasting between 8.00 a.m. and 10.00 a.m. Sera were separated from the blood

samples that were centrifuged at 1,000 g for 10 min at +4°C. Sera were stored at -20°C for batch measurements. Serum glucose, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) concentrations were assessed using original commercial reagents (Beckman Coulter Ireland Inc., Mervue Galway, Ireland) on an analyzer (UniCel Dx C 800 Synchron Clinical System; Beckman Coulter, Fullerton, Calif., USA). Low-density lipoprotein cholesterol (LDL-C) concentrations were obtained using the Friedwald and Frederickson formula [15]. Serum insulin concentrations were analyzed via the chemiluminescent immuno-metric assay method on an analyzer (Siemens IMMULITE 2000; Siemens Medical Solutions Diagnostics Ltd., Llanberis, UK) with original reagents. The intra-assay coefficient of variation was 5.5% at 7.67 µIU/ml, 4% at 12.5 µIU/ml, 3.3% at 17.2 µIU/ml and 3.9% at 26.4 µIU/ml concentrations. The inter-assay coefficient of variation was 7.3% at 7.67 µIU/ml, 4.9% at 12.5 µIU/ml, 4.1% at 17.2 µIU/ml and 5% at 26.4 µIU/ml concentrations. Serum glucose and insulin were used for calculation of the homeostasis model assessment-IR (HOMA-IR) as follows: fasting insulin (mIU/ml) × fasting glucose (mg/dl)/405. The TC:HDL-C and LDL-C:HDL-C ratios were taken into consideration as atherosclerotic markers [16, 17].

Statistical Analysis

Analyses were performed using SPSS version 11 software for Windows (SPSS Inc., Chicago, Ill., USA). All data are expressed as means ± SD. $p < 0.05$ was considered statistically significant. The normality assumption for continuous variables was tested using the Kolmogorov-Smirnov test. Differences in the means of normally distributed variables were evaluated using a t test, whereas a Mann-Whitney U test was used for non-Gaussian variables. Categorical variables were assessed using the χ^2 test. Correlation analysis was done with the Pearson test for variables with a parametric distribution. Spearman's rho coefficient was calculated to examine the relation between HOMA-IR and BP since HOMA-IR was not distributed normally. A logistic regression model was used to analyze any association between obesity and night-time hypertension and biochemical markers. Adjusted OR and their corresponding 95% CI were calculated. Fasting insulin level (FIL), HOMA-IR, TG level, night-time SBP, TC:HDL-C ratio, and LDL-C:HDL-C ratio were included as variables in the multivariate analysis. Age and gender were not included as covariates in the model since frequency matching resulted in similar distributions of these variables in the two groups.

Results

The mean ages of the obese and non-obese children were 12.57 ± 2.74 years and 12.13 ± 2.67 years, respectively. Of the obese subjects, 50% were male and 50% were female. In the control group, there were 18 (47.4%) boys and 20 (52.6%) girls. The difference was not statistically significant ($p = 0.47$).

The anthropometric and biochemical characteristics of the obese and non-obese children are shown in table 1. TG, TC, LDL-C level, TC:HDL-C ratio, LDL-C:HDL-C

Table 1. Anthropometric and biochemical parameters of obese and healthy children

Anthropometric and biochemical parameters	Obese children (n = 38)	Control group (n = 38)	p
Age, years	12.6±2.7	12.1±2.6	NS
Height SDS	0.6±1.1	-0.2±0.9	0.02
Weight SDS	2.5±0.7	-0.4±0.9	<0.001
BMI	28.2±4.8	17.63±2.5	<0.001
BMI SDS	5.3±1.7	-0.14±0.8	<0.001
FBG, mg/dl	83.7±7.4	90.84±7.8	<0.001
FIL, uIU/ml	15.2±9.5	11.82±13.6	0.012 ^a
HOMA-IR	3.2±2.1	2.7±3.2	0.039 ^a
TG, mg/dl	107.2±54.5	75.67±40.9	0.006
TC, mg/dl	163.7±25.6	144.34±24.9	0.001
HDL-C, mg/dl	39.9±7.7	45.21±15.1	NS
LDL-C, mg/dl	101.4±22.5	82.73±21.1	<0.001
TC:HDL-C ratio	4.2±0.9	3.48±1.3	0.006
LDL-C:HDL-C ratio	2.6±0.7	2.02±0.8	0.001

Student's t test. Data are expressed as means ± SD. NS = Not significant; FBG = fasting blood glucose.

^a Mann-Whitney U test.

Table 2. ABP parameters

ABP parameters	Obese children (n = 38)	Control group (n = 38)	p
Daytime (8.00 a.m. to 8.00 p.m.)			
SBP, mm Hg	119.4±9.3	111.39±8.5	<0.001
DBP, mm Hg	67.5±6.7	64.0±6.3	0.022
Night-time (12.00 a.m. to 6.00 a.m.)			
SBP, mm Hg	110.9±9.2	103.6±9.4	0.001
DBP, mm Hg	60.7±7.3	58.2±6.1	NS
24 h (8.00 a.m. to 8.00 a.m.)			
SBP, mm Hg	116.13±9.3	108.3±8.34	<0.001
DBP, mm Hg	65.05±6.62	61.9±5.49	0.023

Data are expressed as means ± SD. NS = Not significant.

ratio, FIL and HOMA-IR were significantly higher in obese children than in non-obese children ($p < 0.05$). Daytime SBP and DBP, night-time SBP, 24-hour SBP and DBP in obese children were significantly higher compared to the values in non-obese children ($p < 0.05$) (table 2).

Twelve (31.6%) obese and 8 (21.1%) non-obese children had a decrease in SBP and DBP <10% and were thus defined as non-dippers. The frequency of non-dippers

was not different between the obese and control groups ($p = 0.435$). No differences were found between dippers and non-dippers with respect to body composition parameters, or the IR index or the lipid profile. The TC:HDL-C and LDL-C:HDL-C ratios of dippers (3.41 ± 0.85 and 1.98 ± 0.71 , respectively) were significantly lower compared to those of non-dippers (4.0 ± 1.22 and 2.45 ± 0.81 , respectively) ($p = 0.032$ and $p = 0.018$, respectively).

Eleven (28.9%) obese and 7 (18.4%) non-obese children had night-time DBP at or above the 95th percentile, and 17 (44.7%) obese children and 13 (34.2%) non-obese children had night-time SBP at or above the 95th percentile. The frequency of night-time SBP and DBP at or above the 95th percentile was not significantly different between obese and non-obese children ($p = 0.348$ and $p = 0.280$, respectively). There were no significant differences in IR parameters and lipid profiles between children with night-time SBP at or above the 95th percentile and children with night-time SBP below the 95th percentile for obese, non-obese and all children separately ($p > 0.05$, data are not shown). Atherosclerotic parameters (TC:HDL-C and LDL-C:HDL-C ratios) in children with night-time SBP at or above the 95th percentile (4.36 ± 1.15 and 2.74 ± 0.91 , respectively) were significantly higher than the values in children with night-time SBP below the 95th percentile (3.68 ± 1.12 and 2.19 ± 0.74 , respectively) ($p = 0.029$ and $p = 0.013$, respectively).

The significant positive correlations of BMI with daytime, night-time and 24-hour SBP ($r = 0.45$, $r = 0.44$, $r = 0.47$, $p < 0.05$, respectively) were stronger than the correlations of BMI with daytime, night-time and 24-hour DBP ($r = 0.27$, $r = 0.26$, $r = 0.31$, $p < 0.05$, respectively). HOMA-IR was positively moderately correlated with night-time SBP ($r = 0.31$, $p = 0.007$). There were moderately positive significant correlations between LDL-C levels, TC:HDL-C and LDL-C:HDL-C ratios and night-time, daytime and 24-hour DBP and SBP ($p < 0.05$). Fasting blood glucose, FIL, HOMA-IR, TG level, night-time SBP, TC:HDL-C ratio and LDL-C:HDL-C ratio were included in the logistic regression model. The statistically significant variables were LDL-C:HDL-C ratio and night-time SBP. LDL:HDL ratio and night-time SBP were significantly positively associated with being obese in adolescents (OR 6.54, 95% CI 1.15–37.07, $p = 0.03$, and OR 1.1, 95% CI 1.01–1.19, $p = 0.02$, respectively).

Discussion

Our study demonstrated that night-time hypertension is more common in all children and, based on ABP consistency with Aguilar et al. [18], the risk of ambulatory night-time systolic hypertension increased significantly with the degree of obesity. Babinska et al. [19] also reported that the BMI is associated with the severity of ambulatory hypertension, similar to our findings. Additionally, Babinska et al. [19] showed that BMI is associated with an increase in daytime systolic and diastolic hypertension in obese children. We found that elevated night-time SBP was associated with an increased risk of being obese. Additionally, we demonstrated significantly higher LDL-C:HDL-C and TC:HDL-C ratios in subjects with night-time hypertension. An elevated LDL-C:HDL-C ratio is associated with an increased risk of being obese. These results suggest that elevated LDL-C:HDL-C ratios and elevated TC:HDL-C ratios may be risk factors for night-time hypertension and elevated LDL-C:HDL-C ratios and night-time SBP increase the risk of being obese. In a previous study, it was demonstrated that TG/HDL-C, which was not assessed in the present study, is a useful marker for hypertension [20].

Traditionally, the assessment of hypertension in children has relied on office blood BP measurements. However, office BP measurements may be misleading for the diagnosis of hypertension, due to the white coat and masked hypertension phenomena in children, as observed in adults [21]. Masked hypertension is a clinical condition in which the office BP is normal but ABPM shows hypertensive values. The largest studies about masked hypertension in healthy children, performed by Lurbe et al. [22], reported a prevalence of 7.6% among 592 children aged 6–18 years. These results suggest that masked hypertension could be common in children and adolescents. Some studies have shown that masked hypertension is associated with an increased risk of left ventricular hypertrophy. Masked hypertension can be diagnosed only via ABPM [23]. In this study, we found that obese children with normal office BP had higher ABP values than non-obese children, confirming the previous findings of Lurbe et al. [23] and Aguilar et al. [18]. These results suggest that the presence of obesity may also increase the requirements of identifying ABPM patterns.

It is possible to record BP during habitual daily activities and sleep while performing ABPM. A decrease (dip) in BP during sleep occurs in normotensive children and adolescents. In some individuals, so-called 'non-dippers', BP does not fall at night. They have a higher risk of car-

diovascular and cerebrovascular events than do their dipping counterparts [5, 24]. Our results revealed that the rates of loss at nocturnal reduction in both DBP and SBP were similar in obese and non-obese children and adolescents. Both anthropometric and lipid parameters, except LDL-C:HDL-C and TC:HDL-C ratios, did not differ between dippers and non-dippers in the present study. These results suggest that high LDL-C:HDL-C and TC:HDL-C ratios may be indicators of the presence of non-dippers in children and adolescents.

As in our study, overweight and obese children are more likely to have lipid abnormalities compared to healthy normal-weight children [25]. However, the rates of abnormal lipid levels were high among overweight children with both office hypertension and normal BP as reported in previous studies [25, 26]. This is similar to our finding in which there was no significant difference in lipid levels between subjects with both night-time hypertension and normal BP. However, positive correlation between LDL-C levels, atherosclerotic markers (LDL-C:HDL-C and TC:HDL-C ratios) and night-time and daytime SBP and DBP demonstrates that the assessment of lipid levels is also important for the presence of night-time hypertension in children and adolescents. Another parameter associated with hypertension is IR, determined by HOMA. Although HOMA levels were significantly

higher in obese adolescents than in non-obese adolescents, they did not differ between adolescents with and without night-time hypertension. We did not evaluate the rate of IR with HOMA in the groups. We found a relationship between HOMA and night-time hypertension. Lurbe et al. [27] demonstrated the contribution of IR to the elevation of night-time BP by dividing groups of children and adolescents using HOMA.

This study has some limitations. We revealed that elevated HOMA and LDL-C:HDL-C and TC:HDL-C ratios could be indicators for night-time hypertension. However, we could not present the cutoff value for these parameters as an indicator for night-time hypertension because of the small sample size of our study. A larger sample size is needed to estimate the cutoff value for these parameters.

Conclusion

Normotensive obese children had higher ABP parameters. A high LDL-C:HDL-C ratio and night-time SBP were associated with an increased risk of being obese. High LDL-C:HDL-C and TC:HDL-C ratios in children and adolescents may be risk factors for night-time hypertension.

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