

## Urinary markers of renal damage in hypertensive children diagnosed with ambulatory blood pressure monitoring

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Primary hypertension is the most important risk factor for chronic kidney disease in adulthood. However, the role of hypertension in kidney damage in childhood is not known exactly. The aim of this study was to evaluate the ambulatory blood pressure measurements of healthy children diagnosed as hypertensive with routine office blood pressure monitoring and to investigate the effects of primary hypertension on the kidney. Fifty-six patients who had blood pressure higher than 90<sup>th</sup> percentile during their well-child follow-up and 27 healthy children with normal blood pressure were included in the study. Twenty-four hour blood pressure measurements were recorded for all the patients. Microalbumin and N-acetyl- $\beta$ -D-glucosaminidase (NAG) levels in the 24-hour urine were determined in the study groups. According to the results of ambulatory blood pressure measurements, 52% of the patients were diagnosed as white coat hypertension. The patients and the white coat hypertensive group had higher levels of urinary NAG than the control group. No significant difference was found in the levels of urinary microalbumin excretion between the primary hypertension and control groups. It was thought that ambulatory blood pressure measurement was necessary for the true diagnosis of hypertension in children, and further, that primary and white coat hypertension had effects on kidney damage in childhood. It is suggested that urine NAG excretion might be used as an early sign of hypertension-induced renal damage.

**Key words:** children, hypertension, ambulatory blood pressure monitoring, renal damage, N-acetyl- $\beta$ -D-glucosaminidase.

The global obesity epidemic is leading to a shift in the blood pressure (BP) distribution toward increasing levels in children and adolescents. Accurate assessment and management of high BP is essential for the prevention of target organ damage. Over the past 15 years, ambulatory blood pressure monitoring (ABPM) has become increasingly recognized as a valuable tool for the investigation of pediatric hypertension. ABPM, which can more precisely characterize changes in BP throughout daily activities, has been found to be superior to office BPM (OBPM) in predicting cardiovascular morbidity and mortality<sup>1-3</sup>. ABPM in adults is also more strongly correlated with renal damage than OBPM<sup>2</sup>.

Urinary N-acetyl- $\beta$ -D-glucosaminidase (NAG) and microalbuminuria are the main biochemical

markers of renal damage. Microalbuminuria, urinary excretion of albumin of 30-300 mg/24 hours, is usually associated with elevated systolic and diastolic BP. In adults, microalbuminuria is present in 6-40% of patients with primary hypertension and is a powerful independent predictor of mortality and cardiovascular and renal morbidity in hypertensive patients<sup>4</sup>. In contrast, data on the prevalence of microalbuminuria in hypertensive pediatric patients are very scarce. NAG is a lysosomal enzyme (molecular weight of 130 kD) that is synthesized by the renal proximal tubular cells and excreted in the urine. The causes of increased NAG activity in the urine of hypertensive patients remain unclear.

The aim of this study was to evaluate the ABP measurements of healthy children diagnosed

as hypertensive with routine OBPM and to investigate the effects of primary hypertension on the kidney.

## Material and Methods

### Subjects

Patients (n=56, 29 boys, 27 girls) who had BP higher than the 90<sup>th</sup> percentile during their well-child follow-up and children with normal BP (n=27, 15 boys, 12 girls) were included in the study. The mean age of the patients was 10.4±3.8 (5-17) years and of the control group was 10.9±2.6 (7-16) years. Three BP measurements were performed with a standard clinical sphygmomanometer using a cuff appropriate to the upper arm size in all hypertensive children and controls. The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents was used for the reference values for the casual OBPM<sup>5</sup>. On the basis of these measurements, the group with stage 1 and 2 hypertension and the group with prehypertension were selected.

All patients underwent the same workup for secondary causes of hypertension, which included determination of body mass index (BMI), serum thyroid hormone, glucose, cholesterol, urea and creatinine levels, heart echocardiography, renal ultrasound with Doppler, and urinalysis. Patients with secondary forms of hypertension were subsequently excluded from the analysis. Patients with no identifiable causes of hypertension were labeled as essential hypertension. None of the patients included in this study was using antihypertensive drugs as angiotensin-converting enzyme (ACE) inhibitors. Weight and height were measured in each child and BMI was calculated as weight (kg)/height (m<sup>2</sup>). Overweight was defined as BMI >95<sup>th</sup> percentile.

### Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) was performed using the oscillometric Welch Allyn-24-hour ABP Monitor, ver. 12. The monitors were programmed to measure the BP every 20 minutes during the day and every 30 minutes at night. Standard deviation scores (SDS) according to gender and height were calculated as systolic and diastolic arterial BP during the daytime and nighttime and as 24-hour mean BP values using the method of Soergel et al.<sup>6</sup>, and the results were evaluated according to the reference values reported

by Wühl et al.<sup>7</sup> The nocturnal BP decrease (dipping) was calculated as the day-night BP difference expressed as a percentage of the daytime BP mean. The non-dipping phenomenon was diagnosed as dipping of the systolic or diastolic BP of <10%. BP systolic and diastolic loads during the daytime and nighttime were derived for each child from the 24-hour recording. These were calculated as the percentage of readings exceeding the child's 90<sup>th</sup> percentile by sex, age, and height.

For staging of ABP levels in children, the modified criteria of Lurbe et al.<sup>3</sup> were used. According to these criteria, normal BP was defined as <95<sup>th</sup> percentile by casual BP, <95<sup>th</sup> percentile by ABPM and <25% systolic BP load. White coat hypertension was defined as casual BP >95<sup>th</sup> percentile in the medical setting, ABPM <95<sup>th</sup> percentile and <25% systolic BP load. Masked hypertension was defined as casual BP <95<sup>th</sup> percentile in the medical setting, ABPM >95<sup>th</sup> percentile and >25% systolic BP load. Prehypertension was defined as casual BP >95<sup>th</sup> percentile in the medical setting, ABPM <95<sup>th</sup> percentile and 25-50% systolic BP load. Ambulatory hypertension was defined as casual BP >95<sup>th</sup> percentile in the medical setting, ABPM >95<sup>th</sup> percentile and 25-50% systolic BP load. Severe ambulatory hypertension was defined as casual BP >95<sup>th</sup> percentile in the medical setting, ABPM >95<sup>th</sup> percentile, and >50% systolic BP load.

### Biochemical Analysis

After 24-hour urine collection, a specimen of about 15 ml was frozen at -20°C until analysis. Before the analysis, the specimen was thawed at room temperature. The urinary NAG levels were measured by a spectrophotometric method with a colorimetric kit. Albumin in the urine specimen was assayed by immunoturbidimetric method.

### Ethics

Informed consent was obtained from each child and their parents, and the study protocol conformed to the ethical guidelines. The study was approved by the ethics committee in our institutions.

### Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) ver. 19 software package. The Kolmogorov-Smirnov test was used to assess the normality of numeric

variables. For the numeric variables that were normally distributed, comparison between two groups was made by the independent sample t test, and descriptive statistics were shown as mean±standard deviation (SD). For the non-normally distributed variables, comparison between two groups was made by the Mann-Whitney U test and descriptive statistics were shown as median (25<sup>th</sup>-75<sup>th</sup> percentiles). The proportions between certain subgroups were compared using the chi-square test. Correlations between BP SDS values and urine microalbumin and NAG values were tested by the Spearman correlation coefficient. Values of  $p < 0.05$  were considered to be statistically significant.

### Results

Based on the BP measurements using the Korotkoff method, 5 (9%) children were diagnosed as prehypertensive, 11 (19%) as stage 1 hypertension, and 40 (72%) as stage 2 hypertension. All children in the control group had normal BP values.

After performing ABPM in the hypertensive children according to OBPM, white coat hypertension was found in 52%, prehypertension in 25%, and ambulatory hypertension in 23%. No masked hypertension was found in the control group. Forty percent of the children with normal mean BP levels had elevated BP loads.

The mean daytime systolic and diastolic BP and day-night systolic BP loads of the patient group were higher than in the control group (Table I). Nighttime systolic and diastolic BP dipping was not different between the children with primary hypertension and the control group.

Microalbuminuria was present in 9% of hypertensive children and in 25% of healthy controls. The median urinary albumin excretion in children with hypertension was not significantly different than in the control group (Table II). Microalbumin levels were lower in the patients with high BP load than in the control group. No significant correlation was found between urinary albumin excretion and nighttime and daytime systolic and diastolic BP loads. A mild positive correlation was found between urinary albumin excretion and nighttime systolic ( $r=0.339$ ,  $p=0.011$ ) and diastolic ( $r=0.349$ ,  $p=0.009$ ) BPs and daytime systolic ( $r=0.331$ ,  $p=0.014$ ) and diastolic ( $r=0.384$ ,  $p=0.004$ ) BPs. There was no statistically significant correlation between

urinary albumin excretion and BP dipping.

Urinary NAG excretion was found to be significantly increased in children with hypertension than in the control group (Table II). In the patient group, there was a positive correlation between urinary NAG excretion and nighttime mean diastolic BP ( $r=0.32$ ,  $p=0.015$ ) and nighttime diastolic BP load ( $r=0.34$ ,  $p=0.01$ ) (Figs. 1, 2). There was no statistically significant correlation between urinary NAG excretion and BP dipping. There was no statistically significant correlation between urinary NAG and microalbumin excretions.

The median urinary NAG excretion was found to be significantly increased in children with white coat hypertension than in the control group. However, urinary albumin excretion was similar in the two groups (Table III). The median urinary NAG excretion was found to be increased in children with ambulatory hypertension and prehypertension when compared to the control group. Urinary albumin

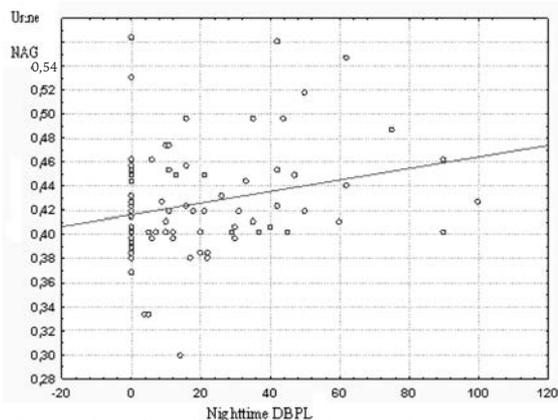


Fig. 1. Correlation between urine NAG excretion and nighttime diastolic blood pressure load.

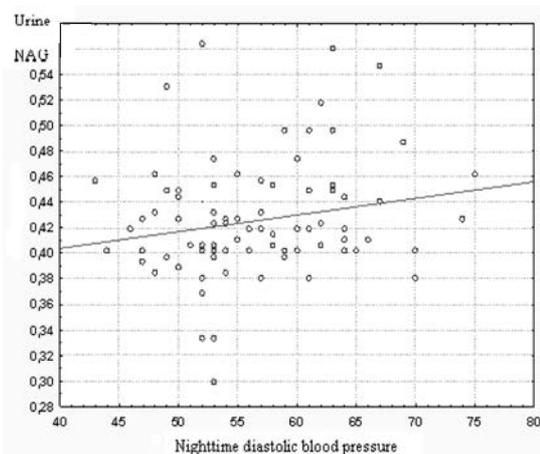


Fig. 2. Correlation between urine NAG excretion and nighttime diastolic blood pressure.

excretion was not different (Table III).

According to BMI, 32% of the children were obese. Daytime systolic BP load was found to be increased in obese children compared to normal-weight children. Mean daytime and nighttime systolic and diastolic arterial BPs and distribution of dipping status were not different between obese and normal-weight children. There were positive correlations between daytime ( $r=0.399$ ,  $p=0.002$ ) and nighttime ( $r=0.379$ ,  $p=0.04$ ) mean systolic BPs, daytime systolic BP load ( $r=0.30$ ,  $p=0.025$ ) and BMI. The median urinary albumin and NAG excretion in obese children was not different than in normal-weight children. However, there was a positive correlation between microalbuminuria and BMI ( $r=0.28$ ,  $p=0.033$ ). No significant correlation was found between urine NAG and BMI.

### Discussion

Ambulatory blood pressure monitoring (ABPM) has become more widely used in the assessment of elevated BP in children. In this study, ABPM results were evaluated according to the reference values reported by Wühl<sup>7</sup> and staged according to the classification of ABP levels in children modified by Lurbe<sup>3</sup>. Although the OBPM results showed 91% of the children as having stage 1 and 2 hypertension and 9% as having prehypertension, ABPM results of the same patients revealed that 52% had white coat hypertension, 25% were prehypertensive and

23% had ambulatory hypertension. Elevated BP loads were found in 40% of the children in the control group, who had normal BP values and normal mean BP levels with both OBP measurement and ABPM, respectively. To our knowledge, there has been no description about children who have high BP loads while having both casual BP and ABPM values <95th percentile. We believe that new studies about such children are needed.

Ambulatory blood pressure monitoring (ABPM) was helpful to identify patients with white coat hypertension. The accurate diagnosis of white coat hypertension in children was particularly important because detection of elevated BP often results in expensive and invasive diagnostic procedures to detect any underlying disease. It was suggested that the ratio of white coat hypertension was higher in children than in adults<sup>8</sup>. Subsequent studies have shown that the prevalence of white coat hypertension in children ranged between 12.9% and 88% depending on the criteria used<sup>1</sup>. Floriańczyk et al.<sup>9</sup> investigated 212 children with elevated BP and 81 healthy controls. With the use of standard BP measurement, 79.2% of children were diagnosed as hypertensive and the remaining 20.8% as prehypertensive. When the ABPM was used, arterial hypertension was diagnosed in 67.4% of the cases and white coat hypertension in the remaining 32.6%. Masked hypertension was diagnosed in 8.7% of the control group. In another

**Table I.** ABPM Parameters in Patients with Hypertension and the Control Group

Mean blood pressure	Patient (n=56)	Control (n=27)	P
Daytime systolic (mmHg)	113.0±11.0	105.8±8.1	0.001*
Daytime diastolic (mmHg)	65.5±8.4	61.4±6.2	0.031*
Nighttime systolic (mmHg)	103.0±11.0	99.4±8.4	0.145
Nighttime diastolic (mmHg)	56.4±7.1	56.7±6.3	0.700
Daytime SBPL (%)	18.7±22.0	8.8±13.0	0.018*
	10.5 (2.2-27.7)	0 (0-16)	
Daytime DBPL (%)	9.7±15.0	3.6±5.00.080	
	4 (0-11)	0 (0-7)	
Nighttime SBPL (%)	23.4±26.1	9.9±16.8	0.005*
	14(0-38)	0 (0-14)	
Nighttime DBPL (%)	20.4±25.2	16.5±19.7	0.700
	10 (0-38)	12 (0-29)	

ABPM: Ambulatory blood pressure monitoring. DBPL: Diastolic blood pressure loads. SBPL: Systolic blood pressure loads. \* $p<0.05$ .

study, Morić et al.<sup>10</sup> found the ratio of white coat hypertension as 21.1%. In our study, the ratio of white coat hypertension was found as 52%. The respectable high ratio of white coat hypertension denoted the importance of ABPM.

Masked hypertension has been found to be prevalent in the pediatric population, ranging from 7.6 to 26%<sup>1</sup>. Children with masked hypertension were more likely to have higher BMIs, a parent with hypertension, and higher prevalence of left ventricular hypertrophy compared with normotensive controls<sup>1</sup>. In our study, no masked hypertension was found in the control group. It was thought that masked hypertension levels were lower in children, especially those with normal BMIs.

Non-dipper BP was found correlated with end-organ damage in adults<sup>11</sup>. Some studies have shown 30% of children as being non-dipper physiologically<sup>1,12</sup>. A high ratio of non-dipping was found both in hypertensive children and healthy controls, as 50% and 59%, respectively. No correlation was found between the ratio of non-dipping and NAG levels. These results gave rise to the thought that non-dipper BP in children was physiologic and had no effect on renal damage.

The kidney is one of the organs affected early in the course of hypertension. Urinary NAG and microalbuminuria are the main biochemical markers of renal damage. The kidney undergoes parenchymatous alterations as basement membrane thickening, hyalinization and focal and global glomerular sclerosis with areas of tubular atrophy and interstitial fibrosis. Vascular changes in the intima and elastic layer of the interlobular arteries, with subendothelial deposit of hyaline material in the afferent arterioles, also occur<sup>13</sup>. Microalbuminuria, urinary excretion of albumin of 30-300 mg/24 hours, is usually associated with elevated BP<sup>13</sup>. In essential hypertensives, an increased transglomerular passage of albumin may result from several mechanisms, including

hyperfiltration, glomerular basal membrane abnormalities, endothelial dysfunction, and nephrosclerosis<sup>14</sup>. The purpose of this work was to observe the excretion of microalbumin and NAG in children with primary hypertension.

N-acetyl-β-D-glucosaminidase (NAG) is a high molecular weight (130 kD) lysosomal enzyme. It cannot pass into glomerular ultrafiltrate due to its high molecular weight. Thus, urinary NAG is of renal origin. This enzyme shows high activity in renal proximal tubular cells, and leaks into the tubular fluid as the ultrafiltrate passes through proximal tubules. It is the most active of glycosidases found in the lysosomes in the proximal tubule. When proximal tubular cells are injured, urinary NAG level increases<sup>15</sup>. The causes of increased NAG activity in the urine of hypertensive patients remain unclear. Urinary excretion of NAG, first studied by Mansell et al.<sup>16</sup> in 1978, is elevated in 23-36% of patients with stage 1 hypertension. Alderman et al.<sup>17</sup> reported that the urinary determination of NAG in hypertensive patients is an index of renal damage. Maldonado-Martín et al.<sup>13</sup> showed that microalbuminuria and urinary excretion of NAG were higher in hypertensive patients than in controls. Simon et al.<sup>18</sup> showed that serum and urinary NAG activity was increased in hypertensive patients but was not increased in the control group. Xu et al.<sup>19</sup> showed that among the hypertensive patients, urinary excretion rates of NAG were increased compared with the healthy controls. Lisowska-Myjak et al.<sup>20</sup> showed that in normoalbuminuric and microalbuminuric patients with essential hypertension, renal impairment measured by glomerular filtration rate was related to increased urinary NAG activity. They suggested urinary NAG activity as an independent promising candidate marker for use in assessing the progression of early renal impairment in patients with hypertension. However, other authors found normal levels of NAG in mild hypertension<sup>21</sup>. Narkiewicz et al.<sup>22</sup> designed a study to evaluate the urinary

**Table II.** Urine Microalbumin and NAG Excretion in Patients with Hypertension and the Control Group

	Patient	Control	p
Urine microalbumin (μg)	13.80±1.60	22.50±4.60	0.091
	10(6-18)	12(7-32)	
Urine NAG (IU/L)	0.4347±0.0058	0.4063±0.402	<0.001*
	0.427(0.406-0.453)	0.402(0.385-0.415)	

NAG: N-acetyl-β-D-glucosaminidase.

**Table III.** Urine NAG and Microalbumin Excretion in Classifications According to ABPM Data

	White coat hypertension (n=29)	Prehypertension (n=14)	Ambulatory HT (n=13)	Control (n=27)
Microalbumin ( $\mu$ g)	11.60 $\pm$ 10.30	17.21 $\pm$ 16.51	15.23 $\pm$ 9.95	22.50 $\pm$ 23.70
	7 (5-15.5)	11.5 (6.7-21.2)	4 (8.5-20)	112.5 (7.5-32)
Urine NAG (IU/L)	0.43 $\pm$ 0.35*	0.43 $\pm$ 0.033*	0.45 $\pm$ 0.066*	0.40 $\pm$ 0.04
	0.427 (0.404-0.451)	0.419 (0.405-0.45)	0.44 (0.401-0.502)	0.402 (0.385-0.415)

ABPM: Ambulatory blood pressure monitoring. HT: Hypertension. NAG: N-acetyl- $\beta$ -D-glucosaminidase.

excretion of albumin and NAG activity in juvenile borderline hypertension and to examine the relationship between these variables and ambulatory BP level and variability. Both urinary C-peptide and albumin excretion were significantly increased in comparison to those of the controls, while NAG activity did not differ significantly between the two groups<sup>22</sup>. To our knowledge, there were no data about urinary NAG excretion in primary and white coat hypertension diagnosed by ABPM in children. Our study showed that urinary NAG excretion was significantly increased in hypertensive children diagnosed with ABPM and also in children with white coat hypertension compared to the control group. It is thought that urine NAG excretion could be used as an early maker of hypertension-induced renal damage in both primary and white coat hypertension in children. In the study group, positive correlations were found between urinary NAG excretion and nighttime mean diastolic BP and nighttime diastolic BP load. It was thought that diastolic BP might play an important role in the renal damage.

In patients with hypertension, microalbuminuria was defined as a urinary albumin excretion rate >30 mg/24 hours. Data on the prevalence and significance of microalbuminuria in pediatric hypertensive patients are very scarce. To date, of the studies that have investigated urinary albumin excretion in children with primary hypertension, the results have shown the prevalence of microalbuminuria to range from 3-58%. Assadi et al.<sup>23,24</sup> demonstrated that 58% of the children with primary hypertension in their study had microalbuminuria, with a clear difference in the prevalence of microalbuminuria between children with stage 1 and stage 2 hypertension. Seeman et al.<sup>4</sup> showed that 20% of the children with primary hypertension had pathological microalbuminuria. Our study

showed that microalbuminuria was present in 9% of children in the hypertensive group. However, 25% of children in the control group also had microalbuminuria. In our study, the children with hypertension were not found to have higher urinary albumin excretion than normotensive children. However, the higher microalbumin levels in the control group than in hypertensive children were not statistically significant. High BP load was not found to affect microalbuminuria in the control group.

While urinary albumin excretion was found as a powerful marker to identify adults with risk for cardiovascular disease, limited data in children with hypertension were found. In children and adolescents with type 1 and type 2 diabetes, microalbuminuria was clearly linked to elevated 24-hour diastolic BP, nocturnal BP, loss of nocturnal dip, or increases in BP load<sup>1, 25,26</sup>. According to the results of our study, it was thought the microalbumin should not be accepted as an accurate indicator of early renal damage.

Many studies have demonstrated that the measurement of ABP correlates more closely to target organ damage than the OBP measurement. Most studies have shown that the organ damage accompanying hypertension, left ventricular mass index, and microalbuminuria is more closely related to 24-hour average BP than to OBP<sup>27,28</sup>. Belsha and co-workers<sup>29</sup> assessed the relationship between ABP and urinary albumin excretion. No relationship was found between microalbuminuria and several ABP parameters. In contrast, Lurbe et al.<sup>30</sup> found a positive relationship between microalbuminuria and ABP in a high-risk population such as in type 1 diabetic children. Opsahl et al.<sup>31</sup> showed that urinary albumin excretion was positively correlated with both OBP and ABP, and urine NAG excretions were positively correlated with ABP but not with OBP. Redon et al.<sup>32</sup>

showed that urinary albumin excretion was positively correlated with the means of systolic and diastolic BP. Oliveras et al.<sup>33</sup> showed significant associations of microalbuminuria, reduced estimated glomerular filtration rate, increased nighttime systolic BP, and elevated daytime, nighttime and 24-hour diastolic BP. In our study, an insignificant positive correlation was found between urinary albumin excretion and nighttime systolic ( $r=0.339$ ,  $p=0.011$ ) and diastolic ( $r=0.349$ ,  $p=0.009$ ) BP and daytime systolic ( $r=0.331$ ,  $p=0.014$ ) and diastolic ( $r=0.384$ ,  $p=0.004$ ) BP. No significant correlation was found between urinary albumin excretion and nighttime and daytime systolic and diastolic BP loads. There was no statistically significant correlation between urinary albumin excretion and BP dipping.

Redon et al.<sup>34</sup> showed that urinary albumin excretion was greater in patients with moderate hypertension than in those with mild or borderline hypertension. In our study, urinary microalbumin excretion was not found to be increased in children with white coat hypertension, prehypertension or ambulatory hypertension when compared to the control group. No correlation was found between the degree of hypertension and the urinary microalbumin levels.

The relationship between obesity and essential hypertension is well known. Excess weight is thought to increase intraglomerular capillary pressure, resulting in glomerular hyperfiltration, a permissive environment or condition for end-organ damage. In this setting, hypertension, impaired fasting glucose or diabetes mellitus may provide a second “hit”, causing endothelial dysfunction that leads to microalbuminuria<sup>35</sup>. Nguyen et al.<sup>36</sup> found a prevalence rate of 10.7% for hypertension among obese adolescents. They showed that hypertension is associated with microalbuminuria in overweight adolescents. Sanad et al.<sup>37</sup> detected abdominal obesity in 93.3% of children, and found that the children had a prevalence rate of 16% for hypertension and of 14.7% for microalbuminuria. In our study, 32% of the children were found obese according to BMI. Mean daytime, nighttime, systolic and diastolic arterial BPs, and distribution of dipping status were not different between obese and normal-weight children. However, daytime systolic BP load was found to be increased in obese children compared to normal-weight children. There

were positive correlations between daytime ( $r=0.399$ ,  $p=0.002$ ) and nighttime ( $r=0.379$ ,  $p=0.04$ ) mean systolic BPs, daytime systolic BP load ( $r=0.30$ ,  $p=0.025$ ) and BMI. The median urinary albumin and NAG excretion in obese children was not different than in the normal-weight children. However, there was a positive correlation between microalbuminuria and BMI ( $r=0.28$ ,  $p=0.033$ ). No significant correlation was found between urine NAG and BMI. It was thought that obesity had a more important role than hypertension in the pathogenesis of microalbuminuria.

In conclusion, urinary NAG was thought to be an early marker of renal damage in primary hypertension determined with ABPM. White coat hypertension, which was found in half of the healthy children who were found to be hypertensive with OBPM, was also found to cause renal damage.

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