Added Impact of Obesity and Insulin Resistance in Nocturnal Blood Pressure Elevation in Children and Adolescents

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Added Impact of Obesity and Insulin Resistance in Nocturnal Blood Pressure Elevation in Children and Adolescents

Empar Lurbe, Isabel Torro, Francisco Aguilar, Julio Alvarez, Jose Alcon, Jose Maria Pascual, Josep Redon

Abstract—The aim of the present study was to analyze the relationship between insulin resistance and the ambulatory blood pressure components in obese children and adolescents. Eighty-seven overweight and obese white children and adolescents of both sexes, of European origin from 6 to 18 years of age (mean age: 10.9±2.7 years), were selected. Obesity was defined on the basis of a threshold body mass index z score >2 (Cole’s least mean square method) and overweight with a body mass index from the 85th to 97th percentile. A validated oscillometric method was used to measure ambulatory BP (Spacelabs 90207) during 24 hours. Fasting glucose and insulin were measured, and the homeostasis model assessment index was calculated. Subjects were grouped into tertiles of homeostasis model assessment index. No significant differences in terms of age, sex, and body mass index z score distribution were observed among groups. When adjusted by age, sex, and height, nocturnal systolic blood pressure and heart rate were significantly higher in subjects in the highest homeostasis model assessment index tertile (>4.7) as compared with those of the other groups, whereas no differences were observed for awake systolic blood pressure or heart rate. Whereas body mass index z score was more closely related with blood pressure and heart rate values, waist circumference was strongly related with insulin resistance. Moreover, both waist circumference and insulin resistance were mainly associated with higher nocturnal but not with awake blood pressure. The early increment of nocturnal blood pressure and heart rate associated with hyperinsulinemia may be a harbinger of hypertension-related insulin resistance and may contribute to heightened cardiovascular risk associated with this condition. (Hypertension. 2008;51:635-641.)

Key Words: obesity ■ insulin resistance ■ nocturnal blood pressure ■ heart rate ■ children ■ adolescents

The prevalence of obesity is continuously increasing among children.1,2 The adverse effects of weight gain on metabolic and cardiovascular function and the association of weight gain with a higher incidence of health problems later in life represent major issues in health care, which have generated great concern over the last few years.3-6 Indeed, considering the increasing tendency for obesity to appear during childhood and to track, to some extent, into adult life,7,8 as well as the firmly established relationships among obesity, type 2 diabetes, and hypertension in adults, obese children appear to be at particularly high risk of becoming diabetic and hypertensive as they age.9

Blood pressure (BP) values in childhood represent the most important measurable marker of the potential level of cardiovascular risk later in life.10 This strongly supports the importance of performing careful and repeated BP measurements during childhood and adolescence. Solid evidence collected over the last 20 years has demonstrated the high prognostic power of ambulatory BP monitoring (ABPM). Indeed, 24-hour BP values have been significantly better predictors of cardiovascular risk than have casual office BP measurements.11-13

A large proportion of obese subjects have insulin resistance (IR), which represents an insensitivity of the peripheral tissues to the effects of insulin. It is not only a major underlying mechanism in the development of type 2 diabetes associated with obesity15 but is also an independent cardiovascular risk factor.16 The relationship of IR with elevated BP has been recognized for many years, although the role of the operating mechanisms remains partially unresolved. Understanding the early relations among overweight, IR, and BP would appear to be important in developing intervention/prevention strategies. The aim of the present study was to analyze the relationship between IR and the ambulatory BP components in obese children and adolescents, a group prone to develop IR and high BP.

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The study was presented as an abstract to the annual meeting of the American Society of Hypertension, Chicago, Ill, 2007.
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Subjects and Methods

Selection of Study Participants
Obese white children and adolescents of both sexes, ranging from 6 to 18 years of age, were enrolled from the Pediatric Department, Consorcio Hospital General, from those who underwent an assessment of obesity in 2005. Patients with secondary obesity syndromes and/or with acute illnesses were excluded from the study. The study was approved by the ethical committee of the center. Body weight was recorded to the nearest 0.1 kg using a standard beam balance scale with the subjects wearing light indoor clothing and no shoes. Height was recorded to the nearest 0.5 cm using a standardized wall-mounted height board. Obesity was diagnosed when body mass index (BMI; the weight in kilograms divided by the square of the height in meters) exceeded the 97th percentile for age and sex. The extent of obesity was quantified using Cole’s least mean squares method.17 Consequently, obesity was stratified on the basis of a threshold BMI z score of $\geq 2.0$, namely, moderate obesity as a z score of 2.0 to 2.5 and severe obesity as a z score $>2.5$. Subjects with a BMI ranging from the 85th to the 97th percentile of the BMI distribution (BMI z score $<2$) in a normal age-matched reference population, and, therefore, defined as being overweight, were included in the study.17 Waist circumference was measured at the midpoint between the iliac crest and the costal margin in the midaxillary line in standing position at the end of a gentle expiration. Pubertal development was assessed through physical examination according to the Tanner criteria.18 Informed consent was obtained from parents and participants before testing. The study was approved by the ethical committee of the center.

Metabolic Assessment
Metabolic assessment was performed under fasting conditions in the early morning. Peripheral blood samples were obtained to measure glucose by the glucose oxidase method (Beckman Glucose Analyzer, Beckman Instruments), insulin (Pharmacia Insulin radioimmunoassay kit), and lipid profile. The homeostatic model assessment (HOMA) index was calculated by dividing the product of insulin (microunits per milliliter) and glucose (millimoles per liter) by 22.5.19

Office BP Measurements
On the day of ABPM, trained nurses measured the BP and heart rate (HR) of each subject 3 times consecutively in the seated position, at 5-minute intervals, using a mercury sphygmomanometer. This was done following the published recommendations.20 Office BP was taken as the mean of 3 measurements. Office BP had to be persistently greater than or equal to the 95th percentile of the BP distribution in a normal reference population on $\geq 3$ separate occasions to be considered indicative of a hypertensive condition.20

ABPM: Devices and Methods
Validated oscillometric devices were used to measure ambulatory BP (Spacelabs model 90207 and 90217 monitor, Spacelabs, Inc). The appropriate cuff, chosen from the 3 different sizes available, was attached to the nondominant arm. The frequency of automated reading was programmed at 20-minute intervals from 8 AM to 12 AM and at 30-minute intervals from 12 AM to 6 AM. ABPM was performed during a normal weekday that included normal recreational activities. Each recording began between 8:30 AM and 9 AM. 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.

For data analysis, the whole 24-hour, awake (between 8 AM and 10 PM), and sleep (between 12 AM and 6 AM) periods were separately considered. Awake and sleep periods were defined according to fixed, narrow, clock time intervals, which more closely corresponded with the awake and asleep behavioral conditions in all of the subjects. The transition periods between wakefulness and sleep in the morning and evening, respectively, during which BP may undergo rapid changes with important interindividual differences, were excluded.

An average of 63 ± 5 BP measurements during the 24 hours was recorded. The following parameters were calculated for each subject: (1) total number of BP readings; (2) average of systolic BP (SBP), diastolic BP, and HR over the 24-hour, awake, and sleep periods; and (3) circadian BP and HR variability, estimated as the awake:sleep time ratio in systolic and diastolic BP and HR averages.

Statistical Analysis
Values were expressed as means±SEs for each HOMA index tertile. The differences in BP mean values and variability estimates between different the study groups were assessed through ANOVA. Covariance analysis, with current age and sex as covariates, was performed to control for differences in these parameters in each of the HOMA index groups. A Bonferroni’s correction was applied in the case of multiple comparisons. The relationship among BMI z score, HOMA index, and BP values was sought by Pearson’s partial correlation coefficients adjusted by current age, sex, and BMI z score and by plotting the corresponding regression lines. A stepwise multiple regression analysis was performed by using the HOMA index and BP values as dependent variables. Values of $P<0.05$ were set as the minimum level of statistical significance.

Results
Characteristics of the Study Population
From a total 204 subjects invited to participate, a total of 87 (43.5%) young white subjects were included in the study, of which 17 (19.5%) were overweight and 70 (80.5%) were obese. Using the HOMA index, the study population was grouped into tertiles: first tertile <3.1, second tertile between 3.1 and 4.7, and third tertile $>4.7$. The general characteristics of the study population grouped by HOMA index tertiles are shown in Table 1. No significant differences in terms of age, sex, and BMI z score were observed among the groups. A significant difference, however, was observed for height; therefore, all of the comparisons and association analyses were adjusted for height. Although there were no between-group differences found for age and sex distribution, all of the comparisons were adjusted for these characteristics given the importance of these traits in this age group.
Metabolic Profile

The metabolic parameters are shown in Table 2. Grouped by HOMA index tertiles, no differences existed among the groups in terms of fasting glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides, even when there was a trend to have higher triglycerides and lower high-density lipoprotein in the subjects of the third tertile as compared with the other tertiles. Uric acid levels increased across the 3 tertile groups, and there was a statistically significant difference between the first and the third tertile groups. By definition, fasting insulin and HOMA index increased from the first to the third tertile group.

BP and HR Values

The average office and ambulatory BP and HR values for the different study groups, adjusted by sex, current age and height, are shown in Table 3. Compared with the 2 lower HOMA tertiles, individuals with the highest tertile had higher systolic and HR values during the 24-hour and the sleep periods. Even when office and awake SBP and HR were slightly higher in the subjects in the third tertile, as compared with those for the other 2 tertiles, they only achieved statistical significance for office HR. For diastolic BP values, office and ambulatory, both awake and sleep, no differences among the 3 tertile groups were observed. Only 3 children had office BP values higher than the 95th percentile specific for age, sex, and height,20 all of them pertained to the second HOMA index tertile, and 3 had prehypertension. In contrast, 12 had awake BP values higher than the 95th percentile specific for sex and height.21,22 Three were in the first HOMA index tertile, 4 in the second, and 5 in the third.

When circadian variability of SBP, diastolic BP, and HR was analyzed, there was no statistical difference among the tertile groups despite a trend toward lower values in the

Table 1. General Characteristics of the Study Population Grouped by HOMA Index

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First Tertile &lt;3.1</th>
<th>Second Tertile 3.1 to 4.7</th>
<th>Third Tertile &gt;4.7</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>26</td>
<td>33</td>
<td>28</td>
<td>87</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>10 (38.5)</td>
<td>11 (33.3)</td>
<td>16 (58.2)</td>
<td>37 (42.5)</td>
</tr>
<tr>
<td>Age, average (SD), y</td>
<td>9.9 (3.3)</td>
<td>11.1 (2.5)</td>
<td>11.4 (2.9)</td>
<td>10.9 (2.7)</td>
</tr>
<tr>
<td>Range, y</td>
<td>6 to 18</td>
<td>6 to 14</td>
<td>6 to 14</td>
<td>6 to 18</td>
</tr>
<tr>
<td>Weight, average (SD), kg</td>
<td>58.2 (17.6)</td>
<td>69.7 (16.2)</td>
<td>78.2 (14.6)*</td>
<td>69.0 (17.8)</td>
</tr>
<tr>
<td>Height, average (SD), cm</td>
<td>143.4 (16.0)</td>
<td>153.5 (15.9)</td>
<td>157.0 (10.5)*</td>
<td>151.6 (15.3)</td>
</tr>
<tr>
<td>Waist, average (SD), cm</td>
<td>86.3 (8.8)</td>
<td>95.0 (9.4)</td>
<td>98.5 (8.9)*</td>
<td>93.5 (10.5)</td>
</tr>
<tr>
<td>BMI, average (SD), kg/m²</td>
<td>27.7 (3.9)</td>
<td>29.1 (3.1)</td>
<td>31.6 (4.2)*†</td>
<td>29.5 (4.0)</td>
</tr>
<tr>
<td>BMI z score, average (SD)</td>
<td>2.3 (0.4)</td>
<td>2.3 (0.4)</td>
<td>2.3 (0.3)</td>
<td>2.3 (0.4)</td>
</tr>
<tr>
<td>Overweight and obesity distribution, average (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>6 (6.9)</td>
<td>9 (10.3)</td>
<td>2 (2.3)</td>
<td>17 (19.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (13.8)</td>
<td>19 (21.8)</td>
<td>17 (19.5)</td>
<td>48 (55.2)</td>
</tr>
<tr>
<td>Severe</td>
<td>8 (9.2)</td>
<td>5 (5.7)</td>
<td>9 (10.3)</td>
<td>22 (25.3)</td>
</tr>
<tr>
<td>Tanner stage, average (SD)</td>
<td>2.0 (1.4)</td>
<td>2.7 (1.2)</td>
<td>2.8 (1.1)</td>
<td>2.5 (1.2)</td>
</tr>
<tr>
<td>Range</td>
<td>1 to 4</td>
<td>1 to 4</td>
<td>1 to 4</td>
<td>1 to 4</td>
</tr>
</tbody>
</table>

*p<0.05 with the first tertile.
†p<0.05 with the second tertile.

Table 2. Biochemical and Lipid Profile of the Study Population Grouped by HOMA Index

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First Tertile &lt;3.1</th>
<th>Second Tertile 3.1 to 4.7</th>
<th>Third Tertile &gt;4.7</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose, average (SD), mg/dL</td>
<td>87.8 (1.7)</td>
<td>98.7 (10.7)</td>
<td>94.2 (8.6)</td>
<td>93.4 (8.6)</td>
</tr>
<tr>
<td>Total cholesterol, average (SD), mg/dL</td>
<td>169.2 (29.7)</td>
<td>165.3 (28.8)</td>
<td>161.2 (27.1)</td>
<td>165.1 (28.4)</td>
</tr>
<tr>
<td>LDL cholesterol, average (SD), mg/dL</td>
<td>98.8 (23.3)</td>
<td>91.4 (24.5)</td>
<td>91.7 (24.6)</td>
<td>93.7 (24.1)</td>
</tr>
<tr>
<td>HDL cholesterol, average (SD), mg/dL</td>
<td>52.6 (12.8)</td>
<td>54.2 (15.0)</td>
<td>47.1 (8.0)</td>
<td>51.4 (12.7)</td>
</tr>
<tr>
<td>Triglycerides, average (SD), mg/dL</td>
<td>88.8 (40.2)</td>
<td>98.5 (42.1)</td>
<td>115.9 (59.1)</td>
<td>101.3 (48.5)</td>
</tr>
<tr>
<td>Fasting insulin, average (SD), mU/mL</td>
<td>10.0 (3.4)</td>
<td>17.3 (2.9)*†</td>
<td>29.6 (8.9)*†</td>
<td>19.1 (8.7)</td>
</tr>
<tr>
<td>HOMA index, average (SD)</td>
<td>2.1 (0.7)</td>
<td>3.8 (0.4)*</td>
<td>6.8 (2.1)*†</td>
<td>4.2 (2.3)</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.
*p<0.05 with the first tertile.
†p<0.05 with the second tertile.
subjects in the highest tertile (Table 3). No significant differences in the percentage of nondipper subjects were observed among the tertile groups.

**Relationship Among Anthropometric, Metabolic, BP, and HR Parameters**

A significant relationship emerges between the BMI z score and waist circumference and the metabolic parameters adjusted by age and sex. Although both fasting insulin and HOMA index were significantly related to the BMI z score ($r=0.30$, $P<0.01$; $r=0.25$, $P<0.02$, respectively), these metabolic parameters were strongly related to abdominal fat estimated by the waist circumference ($r=0.59$, $P<0.001$; $r=0.53$, $P<0.001$, respectively). In a stepwise multiple regression analysis including age, sex, BMI z score, and waist circumference, waist ($P<0.001$) was the only independent variable related HOMA index explaining the 27% of variance.

The relationships between BP and HR, on the one hand, and fasting insulin, HOMA index, BMI z score, and waist circumference, on the other, are shown in Table 4. The relationship between the 2 anthropometric parameters, BMI z score and waist circumference, and office and ambulatory BPs largely differed. Although BMI z score correlated with 24-hour awake and sleep SBP, waist circumference only correlated significantly with sleep SBP. In a stepwise multiple regression analysis including age, sex, BMI z score, waist circumference, and Tanner scores, the dependent variable awake SBP was related to age ($P<0.001$) and BMI z score ($P<0.001$), explaining the 23% of variance. In contrast, when...
sleep SBP was the dependent variable, the waist circumference (P<0.001) was the only factor related, explaining the 15% variance. For diastolic BP, only office was significantly related to both anthropometric parameters BMI z score and waist.

Office and ambulatory HRs were significantly related to both BMI z score and waist circumference. In a multiple regression analysis, both awake and sleep HRs were mainly dependent for BMI z score (P<0.001 and P<0.001, respectively), explaining the 30% and the 23% of variance, respectively.

A significant positive relationship between fasting insulin and HOMA index with office (0.006), sleep SBP (0.003), and HR (0.004) was observed, after adjusting for age and sex, a relationship that was not observed for awake SBP. The relationship between fasting insulin or HOMA index and sleep SBP was present significantly in both boys and girls, as well as in those younger or older than 10 years of age. With the addition of BMI z score to the model, all of the relationships remained significant, although sleep SBP (0.028) was somewhat reduced. With the subsequent inclusion of waist only sleep SBP became marginally significant (0.06), whereas the remaining relationships remained significant, including office SBP (0.025) and sleep HR (0.036). The relationship between the HOMA index and sleep SBP is shown in Figure 1, and the sleep SBP values in the overweight, moderately obese, and severe obese subjects grouped by HOMA index tertiles are shown in Figure 2.

Taking all of these data into account, whereas BMI z score was more closely related to BP and HR values, waist circumference was strongly related to IR. Moreover, both waist circumference and IR were mainly associated with an increment in nocturnal but not in awake BP.

### Discussion

The key finding of the present study was that high nocturnal BP was associated with an indirect measurement of IR, the HOMA index, in a group of overweight and obese children and adolescents. At the same degree of overweight, the presence of IR increases the sleep BP values. A clear effect of IR on sleep SBP was observed across the BMI range. The link among obesity, IR, and sleep BP was abdominal fatness, because waist circumference was related to fasting insulin, HOMA index, and sleep BP.

The study was performed on a cohort of overweight subjects recruited from an obesity clinic and not, as in previous studies on ambulatory BP, mainly from hypertension referral clinics. Because of this recruitment criterion, the study was, therefore, able not only to recruit overweight subjects with a wide range of BMI values but also to avoid a possible bias toward higher BP values.

Consequently, only 3 subjects were diagnosed with office hypertension at the end of the clinical evaluation. Data from clinical samples, however, may not be representative of the general population, and selection and referral bias may have inflated our estimate. No subjects had been referred because of previously identified abnormalities of glucose metabolism, and only 1 subject had fasting glucose >110 mg/dL.

Insulin levels and HOMA index were used as surrogate markers of IR. Although these measurements can differ in part of the “gold standard” method to assess IR, the hyperinsulinemic clamp, both are clinical useful markers to uncover glucose homeostasis abnormalities in children and adolescents. The HOMA index distribution did not differ from other studies, with 40% of obese and overweight subjects with values >4.37. The HOMA index, however, was divided into tertiles for the analysis, because there were
no data linking particular levels of HOMA to clinical outcomes, so a specific clinical threshold is not yet available.24,25

Several studies have analyzed the relationship among IR, measured by various methods, insulin levels, and BP in children and adolescents.6–26 A role for IR is suggested from the Bogalusa Heart Study, showing an association between persistently elevated fasting insulin and higher levels of BP after 8 years of observation27 and from the Cardiovascular Risk in Young Finns study showing an association between fasting insulin in 3- to 18-year-olds and BP measured 6 years later.28 Although obesity seems to account for the relation between insulin and high BP, it is only, in part, because childhood IR predicts BP values at age 19 years independent of the effects of obesity.29

In the present study a significant relationship was observed by using 24-hour ABPM, a method that permitted a better assessment of BP values. The relationship was clearly found during the nighttime, when the BP was less influenced by external factors. Then, these data support the role of IR in the development of BP elevation, although this may be mediated in part by obesity. For a given degree of overweight, subjects with the highest HOMA index had not only the highest sleep SBP but also the steepest increment across the obesity degrees.

There are several mechanisms operating in the link among obesity, hyperinsulinemia, and BP elevation.30,31 The presence of high sleep BP may result as a consequence of the persistence of sympathetic overdriving, baroreceptor dysfunction, and volume overload. In the presence of IR, overactivity of the central sympathetic nervous system has been demonstrated, contributing to increase peripheral resistance, reduce baroreceptor dysfunction, and increase sodium reabsorption in the kidney. In keeping with this, sleep HR, which was significantly higher in subjects at the highest levels of the HOMA index, can indirectly reflect sympathetic overactivity, although a decrease in parasympathetic activity cannot be ruled out. The differences in HR among the HOMA index tertiles were more easily observed in resting conditions during the sleep period when physical activity was minimal. During activity, the awake period, no statistical differences were observed, although some values tended to be higher. In addition to sympathetic overactivity, hyperinsulinemia may further increase sodium reabsorption with the consequent volume overload during nocturnal recumbence.

Whether the early increment of nocturnal BP and HR associated with hyperinsulinemia can be a harbinger of hypertension-related IR and can contribute to an increment of the cardiovascular risk associated with this condition is an intriguing question. Longitudinal studies have demonstrated that metabolic abnormalities can be detected in subjects prone to a faster increase of BP over time.32 Not only did prehypertensive subjects more frequently show abnormalities in carbohydrate metabolism, but subjects with abnormalities in metabolic components had higher levels of home and office BP.

The possibility of an additive impact of both hyperinsulinemia and nocturnal high BP values on the vascular and renal system needs to be mentioned. The subjects ranking high on the HOMA index and having high values of uric acid tended to have a dyslipemic profile with high triglycerides and low high-density lipoprotein values. The association of hyperinsulinemia and high sleep SBP values was present early in life, pointing to the necessity to detect this situation in overweight and obese children and adolescents as soon as possible. The finding that IR may be acting interactively with obesity suggests that interventions aimed directly at IR, in addition to weight loss, may be required to alter the early development of cardiovascular risk.

The importance of nocturnal BP in the development of BP-induced organ damage has been demonstrated in diabetic subjects12 and in patients with chronic renal disease.33 Moreover, nocturnal BP seems to be a more sensitive prognostic marker for cardiovascular morbidity and mortality in several epidemiologic studies as compared with office BP measurement counterparts.13 Therefore, the abnormal rise in sleep BP may represent not only an early marker of risk, but also an early mechanism, which, operating in the cardiovascular system and in the kidney, amplify the consequences of the IR and hyperinsulinemia.

Clinical Perspectives
The present study extends to show that obesity, particularly in conjunction with IR, has a significant role in children and adolescents in the development of cardiovascular risk factors. It has been possible not only to confirm the primary risk associated with obesity but also to identify an interaction between obesity and IR: the level of risk in overweight subjects with IR is greater than that of obese subjects but not insulin-resistant subjects. Obese children and adolescents with IR seem to be prone to an early elevation of BP, which is observed in resting conditions. The impact of hyperinsulinemia in the future of both BP temporal trends and cardiovascular risk needs to be assessed in prospective studies. The validity of this observation, which is cross-sectional, needs to be followed by the observation of changes in both insulinemia and sleep BP when losing weight and/or improving IR. Considering the existing evidence on the potential cardiovascular risk of high BP and IR, a prompt intervention could result in more effective cardiovascular protection later in life.

Disclosures
None.

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