Accelarated Skeletal Maturation in Children With Primary Hypertension

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Abstract—It is hypothesized that primary hypertension (PH) is a disorder with origins in childhood linked to, at least in part, aberrations of growth and maturation processes. To evaluate the possible relation between the rate of biological maturity and development of PH, bone age (BA) assessments on the basis of dual x-ray absorptiometry–derived hand scans were performed in 54 newly diagnosed children and adolescents with PH and 54 healthy controls matched for body mass index (BMI), age and sex. Chronological age (CA), body height (in centimeters), body weight (in kilograms), BMI (in kilograms per meter squared), and blood pressure were assessed. Healthy controls had a mean BA of 14.7 ± 2.3 years that was not significantly different from their mean CA of 14.2 ± 2.1 years. In the PH group, the BA of 16.0 ± 2.0 years was higher by 1.9 ± 0.9 years compared with their CA of 14.1 ± 2.0 years ($P<0.0001$). The magnitude of acceleration of skeletal maturation (BA-CA) and its prevalence (88.9%) were significantly higher in PH compared with BMI-matched controls (37.0%; $\chi^2=31.4$; $P<0.0001$). BA-CA values of PH patients were higher by 1.24 years in normal weight ($P<0.0001$), 1.80 years in overweight ($P<0.01$), and 1.40 years in obese ($P<0.0001$) subgroups of BMI z score–matched controls. Stepwise regression revealed that predictors of blood pressure status from normotension through prehypertension stages 1 and 2 of hypertension were BA-CA ($\beta=0.530$; $P<0.0.001$), height ($\beta=-0.379$; $P<0.01$), and CA ($\beta=0.298$; $P<0.05$; $R^2=0.43$). In conclusion, irrespective of BMI, advanced biological maturation should be considered as an independent marker for the development of hypertension. (*Hypertension*. 2009;54:00-00.)

Key Words: bone age ∎ hand densitometry ∎ children ∎ hypertension ∎ biological maturity

The idea that primary hypertension (PH) is a disorder of growth with origins in childhood was first introduced by Lever and Harrap in 1992[1] and was based on observations made by Pickering.[2] According to Lever and Harrap,[1] hypertrophy of arterial wall smooth muscle cells and metabolic changes, including insulin resistance, may be at least in part associated with accelerated biological maturation, which together may hypothetically lead to increased blood pressure and the development of hypertension and cardiovascular disease.

Several methods have been established for evaluating biological maturity in growing children and adolescents. Tanner staging is the most widely used method but is not, however, appropriate for evaluation of biological maturity of younger, prepubertal children. In contrast, biological maturation from birth up to young adulthood (0 to 18 years) may be evaluated and monitored using bone age (BA) readings.[3–11] To examine the potential relationship between blood pressure and biological maturation, we used BA assessments as an index of actual biological maturation in hypertensive children and adolescents compared with healthy controls closely matched for absolute body mass index (BMI), age, and sex.

Subjects and Methods

Subjects

Primary Hypertension
The PH group consisted of 54 newly diagnosed and yet untreated white children and adolescents of Polish origin, including 16 girls aged 14.3 ± 1.2 years and 38 boys aged 14.1 ± 2.1 years, admitted consecutively in years 2007–2009 because of a diagnosis of elevated blood pressure and in whom prehypertension or PH was ultimately diagnosed. Specifically, in all of the cases elevated blood pressure was diagnosed during routine school checkups and/or during clinical workup of other complaints. Time from diagnosis of elevated blood pressure to clinic referral was 4 to 8 weeks.

Control Group
Fifty-four healthy, normotensive children and adolescents aged 14.2 ± 2.1 years participated in our study. Healthy subjects with optimal blood pressure values were recruited and evaluated in years 2007–2009 from a larger cross-sectional, school-based study of blood pressure status of children in the Warsaw area. The blood

pressure measurements, as well as anthropometric investigation of children eligible for this study, were held in our center. To avoid any bias caused by potential impact of overweight and obesity on the tempo of growth and maturation, healthy control subjects needed to match strict inclusion criteria. According to an approach used by Lande et al,[12] control subjects were pairwise matched with their PH mates for sex, chronological age (CA; $\pm$0.5 years), and absolute BMI ($\pm$10%).

Blood Pressure Measurements

Casual blood pressure measurements were performed according to guidelines, after 10 minutes of rest in quiet room, in a sitting position using oscillometric device (Datascope, Accutor Plus). The mean of 3 measurements was taken for analysis. According to recent guidelines, arterial hypertension was diagnosed when elevated blood pressure was $\geq$95th percentile for age, sex, and height; found on $\geq$3 blood pressure measurements on 3 different occasions; and confirmed by auscultatory measurements.[13] In all of the cases, hypertension was confirmed by 24-hour ambulatory blood pressure monitoring. Prehypertension and stage 1 and stage 2 of PH were diagnosed during a hospital stay after thorough examination excluding known causes of secondary hypertension according to fourth task force report guidelines.[13] Prehypertensive patients were recruited from those patients in whom hypertension was erroneously diagnosed and who had blood pressure values persistently in range between the 90th and 95th percentiles both in casual and ambulatory blood pressure monitoring measurements.

Ethics

Ethical approval was obtained for the study from the ethics committee of the Children's Memorial Health Institute. All of the subjects or their parents gave written informed consent for participation in the study.

Assessment of BA

A total of 108 left-hand scans of healthy and PH children were performed using dual energy x-ray absorptiometry (DXA; Expert-XL densitometer; GE Lunar). The method of BA rating was described previously.[14–17] Specifically, the resolution of the hand-wrist image generated by the Expert-XL densitometer was 0.0025 cm^2 as an effect of fan-beam technology.[15] Standard procedures provided by the DXA manufacturer (ie, 1-mA fast, 134 kV) were used for measurements. The entrance surface dose was $\leq$8 μSv, equal to $\approx$1 day of background radiation in Poland. The duration of the DXA hand-wrist scan procedure was $\leq$10 seconds. All o the hand-wrist scans were blinded to CA and the subject's name, saved as a standard picture (.tiff formatted), and sent to our qualified observer for BA assessment via the Internet (Figure 1). Each of 108 hand scans was compared with the original series of standard plates obtained from standard hand-wrist radiographs of white Polish girls and boys, published as a reference atlas of skeletal development.[9] The reference radiographs published in the atlas represent the average skeletal development for CA and sex. As in the method by Greulich and Pyle,[7] the BA of all of the subjects was determined by identification of appearances, sizes, and shapes of skeletal maturity indicators (Figure 1). Maturity indicators were visually analyzed by comparison with standards, and the age given to the standard that matched most closely with the evaluated DXA-derived hand-wrist scan was assigned as the BA of the subject. When the appearances lay between 2 standards, a BA between these was given with the precision of 0.5 years.[9,15] The intraobserver variability calculated on the basis of duplicate BA estimations of 50 hand scans was 0.88% for the observer involved in the present study. On the basis of recommendations of our atlas, the rates of maturation in terms of "physiological," "accelerated," and "delayed" BA were defined as follows: differences between BA and CA ranging between -0.9 to $+0.9$ were considered as physiological, BA-CA below -0.9 as delayed skeletal maturation, and BA-CA above $+0.9$ as accelerated maturation.[9]
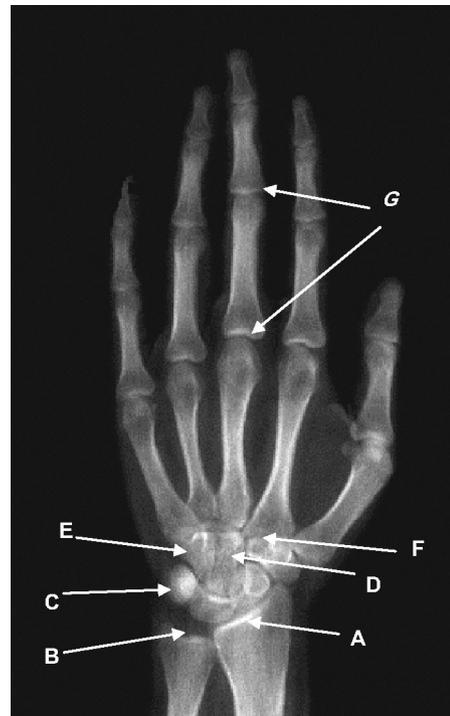
Figure 1. DXA-derived hand-wrist image of a 14-year–old prehypertensive girl, showing the main maturity indicators. According to standards published in the atlas of skeletal development,[13] the presented hand-wrist scan matched most closely to the standard for 18 years of age; therefore, the BA assigned to this image was 18 years. A and B, Radial and ulnar styloid; C, triquetral; D, capitate; E, hamate and hook of hamate; F, trapezoid; G, epiphyses of III phalanx.

Statistical Analysis

Pairs of healthy controls and PH subjects were analyzed as whole groups and in sex-related groups. PH cases were also analyzed according to stage of hypertension in the following groups: prehypertensives (n=11), stage-1 hypertensives (n=31), and stage-2 hypertensives (n=12). Anthropometric parameters such as body height (BH; in centimeters), body weight (BW; in kilograms), and BMI (in kilograms per meter squared) were compared with previously established references using z scores (CA - and sex-matched SDs from the mean observed in a healthy population).[18]

The difference between BA and CA was calculated for each studied patient. The paired t test was performed to assess the significance of differences between BA and CA. ANOVA and the paired t test were used to evaluate the significance of differences between normotensive controls and hypertensive cases, as well as between stages of PH (prehypertensives versus stage 1 versus stage 2).

The χ^2 test was performed to evaluate the significance of differences in the number of subjects with physiological and abnormal differences between CA and BA, with the assumption that differences between BA and CA of <1 year reflect physiological variations of normal skeletal maturation, as recommended by our atlas and others.[7–10,14–17]

In addition, the relation between PH and the rate of skeletal maturation was controlled for the influence of obesity using the BMI z- score–matched subsets of hypertensive cases and normotensive controls. Healthy controls and PH cases were, therefore, grouped and analyzed in the BMI z score ranges as follows: (1) BMI z score less than -1.0 SD, considered a "thin" phenotype; (2) $-1.0 \leq$ BMI z score $\leq +1.0$ SD, considered a "normal" phenotype; (3) $+1.0 <$ BMI z score $< +1.96$ SD, considered an "overweight" phenotype; and (4) BMI z score $\geq +1.96$ SD, considered an "obese" phenotype.

To standardize blood pressure values for age, height, and sex, we used systolic blood pressure (SBP) index (SBPi) and diastolic blood

Table 1. Anthropometric Characteristics of Age-, Sex-, and BMI-Matched Healthy Controls and Hypertensive Cases

Variable	Group	Girls	Boys	Whole Group
CA, y	Healthy	14.28±1.95	14.18±2.16	14.21±2.08
	Hypertension	14.28±1.22	14.08±2.10	14.14±2.01
BA, y	Healthy	14.53±2.05	14.72±2.39	14.67±2.28
	Hypertension	15.84±1.85‡	16.08±2.07§	16.01±1.99§
BA-CA, y	Healthy	0.25±0.73	0.54±0.77	0.45±0.77
	Hypertension	1.56±0.79‡	2.00±0.98§	1.87±0.94§
BH, cm	Healthy	167.6±8.5	171.2±12.2	170.1±11.2
	Hypertension	165.2±7.1	171.5±11.5	169.6±10.8
BW, kg	Healthy	68.3±16.7	75.2±20.7	73.1±19.7
	Hypertension	65.7±15.8	74.8±19.8	72.0±18.9
BMI, kg/m^2	Healthy	24.2±4.8	25.4±5.2	25.0±5.1
	Hypertension	23.8±4.4	25.2±5.2	24.8±5.0
BH z score	Healthy	0.79±0.71	0.49±0.81	0.58±0.78
	Hypertension	0.35±1.26	0.49±0.95	0.44±1.03
BW z score	Healthy	2.08±1.72	1.68±1.63	1.80±1.65
	Hypertension	1.65±1.78	1.68±1.67	1.68±1.70
BMI z score	Healthy	1.62±1.72	1.81±1.72	1.75±1.71
	Hypertension	1.50±1.58	1.77±1.71	1.72±1.67
SBP, mm Hg	Healthy	116.0±11.8	115.6±12.3	115.7±12.1
	Hypertension	129.7±4.0†	136.3±8.5§	134.4±8.0§
DBP, mm Hg	Healthy	69.1±6.5	68.2±6.9	68.4±6.8
	Hypertension	84.3±3.3§	86.1±5.0§	85.6±4.6§
SBPi	Healthy	0.91±0.11	0.89±0.10	0.90±0.10
	Hypertension	1.02±0.03†	1.05±0.07§	1.04±0.06§
DBPi	Healthy	0.83±0.08	0.82±0.08	0.82±0.08
	Hypertension	1.02±0.03§	1.03±0.06§	1.03±0.05§

Statistics for healthy controls vs hypertensive cases are in columns.
†P<0.01.
‡P<0.001.
§P<0.0001.

pressure (DBP) index (DBPi), that is, the ratio of measured blood pressure to the value of the 95th percentile for age, sex, and height.

Pearson correlations were performed for the assessment of a possible relationship of the difference between BA and CA (BA-CA in years) with BH (in centimeters), BW (in kilograms), BMI (in kilograms per meter squared), and respective z scores, as well as with SBP, DBP, SBPi, and DBPi. Finally, multiple stepwise regression was performed to identify predictors of absolute and indexed blood pressure values. All P values <0.05 were considered significant. Results are presented as mean±SD.

Results

Anthropometric Characteristics of Studied Groups
As a result of matching method, PH patients did not differ significantly from their healthy counterparts in terms of CA, BH, BW, BMI, and respective z score values, and in both groups BH z scores were close to 0, that is, close to the value expected in the reference population. In healthy normotensive controls and in PH patients, mean z scores for both BW and BMI were increased and were significantly higher than in the reference population (Table 1; P<0.0001).

When both PH patients and healthy controls were analyzed in sex-related groups, girls and boys did not differ regarding
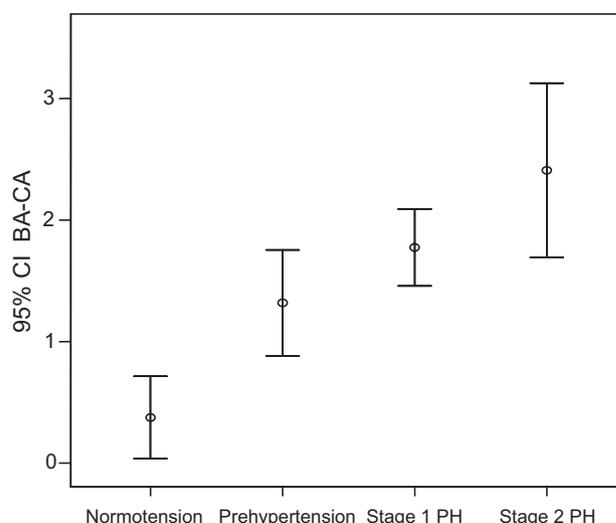
Figure 2. Biological maturity expressed as a difference between BA and CA in relation to blood pressure status. Significant differences between normotensive cases and prehypertensive (P=0.006) and hypertensive patients (P=0.0001), as well as between stage-2 hypertensives and prehypertensives (P=0.009).

absolute BH, BW, BMI, values or respective z scores. Furthermore, there were no significant differences either for absolute values as for z scores of BH, BW, or BMI among the hypertensive groups. As expected, PH patients had significantly higher SBP, DBP, SBPi, and DBPi values compared with those observed in age-, sex-, and BMI-matched healthy counterparts (Table 1; P<0.01 and P<0.0001).

Differences Between BA and CA
In healthy normotensive controls, BA appeared to be not significantly different from CA, showing a mean difference (BA-CA) of 0.25±0.73 years in girls and 0.54±0.77 years in boys (Table 1). In the group of hypertensive cases, the mean CA of 14.14±2.01 years was significantly lower by 1.87±0.94 years than the BA of 16.01±1.99 years (P<0.0001). Furthermore, both in PH girls and in PH boys, the magnitude of acceleration of biological maturation, as assessed by BA-CA values, was significantly greater compared with normotensive BMI-matched controls (P<0.001 and P<0.0001, respectively).

When both PH patients and control cases where analyzed as 1 group, it occurred that BA-CA increased in relation to blood pressure status, that is, it raised significantly from normotension (0.45±0.77 years), through prehypertension (1.59±0.94 years), stage 1 (1.77±0.86 years), and stage 2 hypertension (2.38±1.02 years; Figure 2).

Prevalence of Cases With Abnormal Skeletal Maturation
In healthy controls, accelerated skeletal maturation was observed in 20 cases (37.0%), including 5 girls (31.2%) and 15 boys (39.5%), as assessed by the difference between BA and CA at ≥1 year. Delayed skeletal maturation (BA-CA≤−1) was noted in 3 controls (5.6%), including 2 girls (12.5%) and 1 boy (2.6%).

In the hypertensive group, significantly accelerated skeletal maturation was observed in 48 subjects (88.9%), including 13

Table 2. Skeletal Maturation Rate (BA-CA, in Years) in BMI *z* Score–Matched Subgroups of Healthy Controls and Hypertensive Cases

		BA-CA, y	
BMI *z* Score Range	Phenotype	Healthy Control (n)	Hypertension (n)
BMI *z* score less than −1.0	Thin	0.5 (1)	2.0 (1)
−1.0≤BMI *z* score≤+1.0	Normal	0.26±0.69 (19)	1.50±0.93‡ (19)
+1.0<BMI *z* score<+1.96	Overweight	0.64±0.80 (7)	2.44±0.92† (9)
BMI *z* score≥ +1.96	Obese	0.54±0.82 (27)	1.94±0.89‡ (25)

Statistics for healthy controls vs hypertensive cases are in columns.
†$P<0.01$.
‡$P<0.001$.

girls (81.2%) and 35 boys (92.1%). Delayed skeletal maturation was not observed. The prevalence of cases showing accelerated skeletal maturation was significantly higher in the PH group compared with controls ($\chi^2=31.421$; $P<0.0001$).

Skeletal Maturation in BMI-Matched Subgroups of Healthy Controls and Hypertensive Subjects

Biological maturation rate (BA-CA in years) was analyzed according to BMI *z* score ranges indicating thin, normal, overweight, and obese BMI-based phenotypes. As shown in Table 2, BA-CA values were significantly higher, by 1.24 years in normal ($P<0.0001$), 1.80 years in overweight ($P<0.01$), and 1.40 years in obese ($P<0.0001$) subgroups of PH patients compared with BA-CA values observed in respective subgroups of healthy normotensive controls. In healthy subjects, mean BA-CA values were not significantly different when analyzed among consecutive BMI-based phenotypes. In hypertensives, BA-CA values in normal-weight subjects were significantly lower compared with the values observed in the overweight subgroup ($P<0.05$); other differences were not significant.

Relationships Among the Rate of Skeletal Maturation (BA-CA), Anthropometry, and Blood Pressure Parameters in Healthy Controls and Hypertensive Subjects

In healthy controls, moderate but statistically significant correlations were noted between the BA-CA values and absolute BW ($r=0.36$; $P<0.05$) and BMI ($r=0.31$; $P<0.05$), as well as BW *z* scores ($r=0.31$; $P<0.05$). SBP and DBP were positively associated with BW ($r=0.29$ and $r=0.44$; $P<0.05$), BMI ($r=0.41$ and $r=0.50$; $P<0.05$), and BMI *z* scores ($r=0.40$ and $r=0.43$; $P<0.05$), respectively. SBPi and DBPi values correlated with BMI ($r=0.31$ and $r=0.45$; $P<0.05$) and BMI *z* scores ($r=0.37$ and $r=0.42$; $P<0.05$), respectively.

Among hypertensives, significant correlations were noted for the relationship between BA-CA and BH *z* scores ($r=0.35$; $P<0.05$) and between BA-CA and the stage of hypertension ($r=0.28$; $P<0.05$). When blood pressure was analyzed, significant correlations were noted only between

Table 3. Predictive Models for Hypertension Status (Normal BP, Prehypertension, Stage 1, and Stage 2)

Model	R^2 for the Model	β	P
BA-CA	0.349	0.591	0.0001
BA-CA	0.391	0.645	0.0001
Height		−0.211	0.001
BA-CA	0.430	0.530	0.0001
Height		−0.379	0.001
Chronological age		0.298	0.022

SBP and BH ($r=0.28$; $P<0.05$) and between SBPi and BW, but the latter association was negative ($r=-0.27$; $P<0.05$).

Multivariate linear regression analysis revealed that the magnitude of acceleration of skeletal maturation (BA-CA, in years) was weak but the only predictor of stage of hypertension (normotension, prehypertension, stage 1, and stage 2; $R^2=0.08$; $\beta=0.280$; $P=0.04$). However, when both normotensive and hypertensive children were analyzed together, BA-CA was the strongest predictor of blood pressure status, explaining up to 32% of variability. The others predictors were lower height and greater age (Table 3). Similarly, BA-CA and shorter height were found as predictors of SBPi and DBPi (Table 4).

Discussion

Our main finding is that, in hypertensive children, skeletal maturation, expressed as the difference between BA and CA, was far more advanced than in healthy controls closely matched for age, sex, and both absolute and standardized values of BMI. The second finding is that, when the BA-CA values were analyzed in BMI *z* score–matched subgroups of controls and hypertensives, skeletal maturation, irrespective of the degree of overweight and obesity, was still significantly more accelerated in the PH group. Third, the rate of biological maturation expressed as BA-CA was the strongest predictor of blood pressure status. Our findings are in agreement with results obtained by Katz et al,[19] who demonstrated advanced BA in black children with elevated blood pressure. However, they did not adjust their findings to BMI. Nevertheless, these observations suggest that PH is linked to other underlying biological processes that affect maturity, one expression of which is advanced skeletal maturation. Our findings provide more evidence for the potential association

Table 4. Predictive Models for SBPi and DBPi

Model	R^2 for the Model	β	P
SBPi			
BA-CA	0.192	0.438	0.0001
BA-CA	0.223	0.498	0.0001
Height		−0.233	0.02
DBPi			
BA-CA	0.325	0.571	0.0001
BA-CA	0.349	0.610	0.0001
Height		−0.202	0.03

between abnormally elevated blood pressure and abnormally accelerated biological maturation.

The prevalence of PH cases showing significantly accelerated skeletal maturation was up to ≈2.5 times that in controls (89%). Furthermore, among 54 cases with PH, delayed skeletal maturation was not observed. Moreover, markedly accelerated skeletal maturation was also noted in prehypertensive cases. These findings suggest that, in the entire pediatric population, hypertensives and prehypertensives may have the greatest tempo of biological maturation that is not dependent on BMI.

According to De Luca and Baron,[3] skeletal maturation is regulated by endocrine and paracrine factors, as well as by genetic and nutritional ones, which corresponds with previous findings that the main clinical phenotypes of adolescents with PH are overweight and obesity,[20,21] as well as abnormalities of body composition, including increased fat stores and decreased muscle stores.[22] This is a drawback when keeping in mind that, in the last 2 decades, blood pressure values in the pediatric population have increased in parallel to increased BW.[23,24] However, although blood pressure rise is strictly correlated with BMI, only ≈30% of obese children are hypertensive. It must also be underlined that, in the general pediatric population, increased BW and BMI coincide with accelerated biological maturation and increased BA.[25] That is why we analyzed groups of normotensive and hypertensive children closely matched not only for age and sex but also for BMI. Our findings suggest that overweight/obese children who have accelerated skeletal maturation may be at increased risk of hypertension.

According to Lever and Harrap, "a process governing (somatic) growth raises blood pressure by stimulating cardiovascular growth and maturation . . .."[1] Therefore, abnormalities among growth-promoting factors may lead, on the one hand, to marked acceleration of biological maturation and, on the other, to vascular wall hypertrophy with its known sequelae. This raises the idea of the possible existence of a functional loop between abnormalities of growth-related factors (eg, the IGF1-GH axis), increased tempo of growth and maturation, and vascular hypertrophy and hypertension, and these pathological processes may be exacerbated by increased BW in the subgroup of susceptible individuals. Secondly, if this functional loop exists, it seems important to monitor the tempo of somatic growth using objective methods (eg, BA) to reduce the possible risk of developing PH, especially in cases with abnormally accelerated biological maturation. Finally, structuralized programs focused on the reduction of excessive caloric intake and prevention of obesity, likely to influence both the production and the action of growth-promoting factors (particularly those of the IGF1-GH axis), are needed during the growth period.

Our study has some limitations. The major concerns may be related to the feasibility of DXA-derived hand-wrist images for BA readings; however, our previous studies showed that evaluation of skeletal maturity using DXA images generated by the GE Lunar Expert XL densitometer appeared to be simple, easy, and noninvasive, giving results comparable to the classic, radiography-based method.[19,21] Moreover, BA readings on the basis of DXA-derived hand

scans with the use of a Hologic 4500A densitometer have also been reported.[16] Nevertheless, it should be clearly stated that radiographic images are still the gold standard for BA estimations. Another limitation is related to the quality and current applicability of standard skeletal maturation plates that were obtained in a population born in the 1950s to 1960s.[9] Thus, because of secular trends of accelerated maturation, predominantly resulting from rapid improvement of socioeconomic conditions, the observed discrepancies between CA and BA may be related to the genetic and social backgrounds of the population that formed the basis of the referential atlas. Nevertheless, it should be stressed that both normotensive controls and hypertensive cases were compared with the same referential atlas. Because we evaluated only patients of white origin, our results must be interpreted with caution and cannot be generalized for nonwhites. The other limitation is that, despite the strong statistical significance of our results, as well as strict matching criteria, the number of patients and controls was relatively low. Finally, we performed ambulatory blood pressure monitoring only in hypertensive children and not in normotensive controls. This might cause us to potentially overlook children with masked hypertension.

Perspectives

Our findings indicate that an accelerated rate of biological maturation, independent of sexual development, is a characteristic phenotype of children and adolescents with PH. The precise estimation of the clinical relevance of our results is difficult at present. Implementation of biological maturation assessments, although rather unrealistic in everyday practice, may be crucial for studies focused on the etiopathogenesis of PH during a growth period. It seems that the important clinical problem is the relation among biological maturation, metabolic abnormalities, and target organ damage and the relation between biological maturation and the response to antihypertensive pharmacological treatment. The other perspective is the potential influence of nonpharmacological preventive interventions on the tempo of biological maturation, for example, increases in physical activity levels and dietary modifications.

Disclosures

None.

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