



2017 American Academy of Pediatrics Clinical Practice Guideline: Impact on Prevalence of Arterial Hypertension in Children and Adolescents With Type 1 Diabetes

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OBJECTIVE

In 2017, the American Academy of Pediatrics introduced a new guideline (2017 Clinical Practice Guideline of the American Academy of Pediatrics [AAP 2017]) to diagnose arterial hypertension (HTN) in children that included revised, lower normative blood pressure (BP) values and cut points for diagnosing high BP in adolescents. We studied the impact of the new AAP 2017 on prevalence of HTN in children with type 1 diabetes mellitus (T1DM).

RESEARCH DESIGN AND METHODS

Up to September 2018, 1.4 million office BP measurements in 79,849 children and adolescents (aged 5–20 years) with T1DM were documented in the DPV (Diabetes Prospective Follow-up) registry. BP values of the most recent year were aggregated, and BP values of 74,677 patients without antihypertensive medication were analyzed (median age 16 years and diabetes duration 5.3 years, 52.8% boys). BP values were classified according to AAP 2017 and the references of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) (2011) and the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (fourth report) (2004).

RESULTS

Of the patients, 44.1%, 29.5%, and 26.5% were hypertensive according to AAP 2017, KiGGS, and fourth report, respectively. Differences in prevalence of HTN were strongly age dependent: <10 years, AAP 2017 31.4%, KiGGS 30.7%, fourth report 19.6%; 10 to <15 years, AAP 2017 30.9%, KiGGS 31.2%, fourth report 22.4%; and ≥15 years, AAP 2017 53.2%, KiGGS 28.4%, fourth report 30.0%. Among teenagers ≥15 years, 59.1% of boys and only 46.3% of girls were classified as hypertensive by AAP 2017 but only 21.1%/26% of boys and 36.7%/34.4% of girls by KiGGS/fourth report, respectively.

CONCLUSIONS

Classification of BP as hypertension depends strongly on the normative data used. Use of AAP 2017 results in a significant increase in HTN in teenagers ≥15 years with T1DM, particularly in boys. AAP 2017 enhances the awareness of elevated BP in children, particularly in patients with increased risk for cardiovascular disease.

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In 2017, the American Academy of Pediatrics introduced new guidelines (2017 Clinical Practice Guideline of the American Academy of Pediatrics [AAP 2017]) to diagnose arterial hypertension (HTN) in children and adolescents (1). Extensive data have shown for a long time that a substantial number of children and adolescents with HTN are treated insufficiently or even not at all (1). AAP 2017 incorporates new data on adverse consequences of high blood pressure (BP) in children and contains lower normative BP data and single-value cut points for adolescents. This new guideline is being discussed controversially, as other associations did not follow these recommendations.

Patients with diabetes are at a high risk of developing HTN, diabetic macroangiopathy, and cardiovascular disease. These conditions already start in childhood and adolescence. Previously, we have shown that prevalence of HTN (2) and intima-media thickening (3) are increased in pediatric patients with type 1 diabetes mellitus (T1DM) and are associated with a higher risk for diabetic microvascular complications such as diabetic retinopathy and nephropathy (4). All guidelines for pediatric diabetology recommend regular BP monitoring and strict BP control. However, there is a strong controversy as to what extent BP should be lowered: risk for cardiovascular disease might increase if BP control is too tight, as low BP may cause a J-shaped curve effect with a minimal risk at BP at 130/80 mmHg in subjects with high cardiovascular risk, such as patients with diabetes and hypertension. In a review of 15 reports, Chrysant and Chrysant (5) concluded that in adult patients with T2DM and HTN, lowering glycosylated hemoglobin to <7.0% and BP to <130/80 mmHg did not add any additional benefit and may even be detrimental to patients' health. Other authors show a significant reduction of the risk for stroke and myocardial infarction with intensive BP control, "the lower the better" (6). So, 2017 AAP has revived this discussion with the focus on pediatric patients.

Our objective was to study the impact of the new 2017 AAP on diagnosis and treatment of HTN in pediatric patients with T1DM in Germany, Austria, and Luxembourg.

RESEARCH DESIGN AND METHODS

The study population for the present analysis was selected from the multicenter

DPV (Diabetes Prospective Follow-up) registry. Currently, 456 specialized diabetes centers from Germany ($n = 414$), Austria ($n = 38$), Switzerland ($n = 3$), and Luxembourg ($n = 1$) prospectively document demographic and clinical data of patients with any type of diabetes. Approximately 90% of the pediatric patients with T1DM in Germany and Austria are documented in the DPV registry. As previously described, participating DPV centers transfer locally collected and pseudonymized data semiannually to the University of Ulm, Ulm, Germany, for central analysis and quality assurance. In case of inconsistency or implausibility, data are reported back to the centers for verification or correction. Ethics approval of the DPV initiative has been obtained from the ethics committee of the University of Ulm. Data collection has been approved by the local/national review boards of each participating center (7).

From January 1995 to September 2018, office BP measurements of 77,158 pediatric patients (5–20 years of age) with T1DM were documented in the DPV registry. A total of 74,677 patients did not receive antihypertensive medication and were included into the analysis (Fig. 1).

The patients are all diagnosed with T1DM and visit the diabetes clinic on a regular basis, at least every 3 months, with BP measurements as part of the routine check-up. BP levels were measured in a relaxed, sitting position at the upper arm with proper cuff size using a sphygmomanometer or semiautomated Dinamap (Critikon, Tampa, FL). BP error was reduced by three consecutive readings per occasion as previously described (8). BP values documented during the most recent year of follow-up were aggregated for each individual patient.

BP was classified using normative data from the German Health Interview and

Examination Survey for Children and Adolescents (KiGGS) (9), the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents from 2004 (fourth report) (10), and the new 2017 AAP guideline.

Overt HTN was defined as BP >95th percentile or, for absolute values, systolic BP (SBP) >140 mmHg/diastolic BP (DBP) >90 mmHg for KiGGS and fourth report or >130/80 mmHg for AAP 2017—whatever was lower.

Height and BMIs were compared by SDS values based on the cohort of healthy German children of KiGGS (11).

For adjustment for different laboratory methods, local HbA_{1c} values were mathematically standardized to the Diabetes Control and Complications Trial reference range (4.05–6.05%) using the "multiple of the mean" transformation method (2).

Statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC). The χ^2 test was used to analyze group differences, and multiple testing was performed with the Wilcoxon test. Data are presented as medians and interquartile range (25th–75th percentile) or as percentage as appropriate; $P < 0.05$ (two sided) is considered significant and $P < 0.01$ highly significant.

RESULTS

Characteristics of the Study Population

The median age of the children and adolescents (52.8% male) included in this investigation was 16.0 years, median diabetes duration 5.3 years, and median HbA_{1c} 7.9% (62.8 mmol/mol). Our patients had a median height SDS of 0.08 and BMI SDS of 0.3 and required a median insulin dosage of 0.84 units/kg body wt/day (Table 1). Boys were older than girls, had shorter diabetes duration, and had lower BMI SDS, height SDS, and HbA_{1c} than girls (all $P < 0.0001$, χ^2 test). Insulin dosage did not differ between the sexes ($P = 0.05$) (Table 1).

Based on AAP 2017, 44.4% of our pediatric patients with T1DM were classified as hypertensive, but by KiGGS from 2011 or fourth report from 2004, only 29.5% or 26.5% of our pediatric patients with T1DM were classified as hypertensive, respectively (all $P < 0.0001$, χ^2 test) (Table 2 and Fig. 2).

Boys Versus Girls

The rate of HTN was higher in boys according to the AAP 2017 guidelines

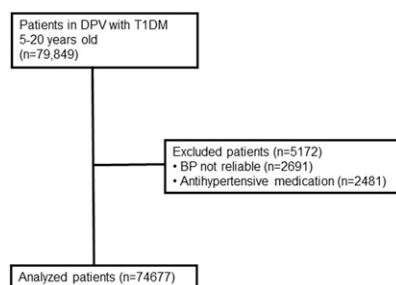


Figure 1—Flowchart for the inclusion of the patients into the investigation.

Table 1—Basic characteristics of the study population and the subgroups

Parameter	Total	Boys	Girls	<i>P</i> _{m vs. f}	<i>P</i> _{5–10 vs.}					<i>P</i> _{10–15 vs.}
					5–10 years	10–15 years	15–20 years	10–15 years	15–20 years	
<i>n</i>	74,677	39,414	35,263		9,341	21,168	44,168			
Male sex	52.8				50.9	52.1	53.5			
Age (years)	16.0 (12.7–17.6)	16.1 (12.8–17.6)	15.9 (12.5–17.6)	<0.00001	8.0 (6.6–9.1)	12.9 (11.6–14.0)	17.5 (16.6–18.4)	<0.00001	<0.00001	<0.00001
BMI SDS	0.30	0.17	0.45	<0.00001	0.28	0.2	0.35	<0.00001	<0.00001	<0.00001
	–0.3 to 0.9	–0.4 to 0.8	–0.2 to 1.0		–0.3 to 0.9	–0.4 to 0.82	–0.3 to 0.9			
Height SDS	0.08	0.07	0.08	<0.00001	0.17	0.14	0.02	0.002	<0.00001	<0.00001
	(–0.6 to 0.8)	(–0.6 to 0.8)	(–0.6 to 0.8)		(–0.5 to 0.9)	(–0.6 to 0.8)	(–0.7 to 0.7)			
Insulin dosage (units/kg body wt/day)	0.84 (0.7–1.0)	0.85 (0.7–1.1)	0.84 (0.7–1.0)	0.05	0.69 (0.6–0.8)	0.85 (0.7–1.0)	0.88 (0.7–1.1)	<0.00001	<0.00001	<0.00001
Age at diabetes onset (years)	9.1 (5.5–12.3)	9.3 (5.6–12.8)	8.8 (5.5–11.8)	<0.00001	5.1 (3.2–6.9)	8.5 (5.3–11.0)	10.7 (7.0–13.6)	<0.00001	<0.00001	<0.00001
Diabetes duration (years)	5.3 (2.4–8.9)	5.1 (2.3–8.7)	5.6 (2.6–9.1)	<0.00001	2.3 (0.8–4.3)	4.2 (1.6–7.3)	6.8 (3.8–10.5)	<0.00001	<0.00001	<0.00001
HbA _{1c} (%)	7.9 (7.1–9.1)	7.9 (7.0–9.0)	8.0 (7.1–9.2)	<0.00001	7.4 (6.8–8.1)	7.9 (7.1–8.9)	8.1 (7.2–9.4)	<0.00001	<0.00001	<0.00001
HbA _{1c} (mmol/L)	63.1 (53.8–75.9)	62.6 (53.4–75.3)	63.6 (54.4–76.5)	<0.00001	57.1 (50.4–64.9)	62.4 (53.6–73.5)	65.4 (55.0–79.3)	<0.00001	<0.00001	<0.00001

Data are presented as median and lower–upper quartile (25–75th percentile) or as percent unless otherwise indicated. *P* < 0.05 is considered significant and *P* < 0.0001 highly significant (Wilcoxon test). Boldface values indicate significant differences: f, females; m, males.

Table 2—Absolute BP and prevalence of HTN in the study population and the subgroups

Parameter	Total	Boys	Girls	$P_{m\ vs.\ f}$	5–10 years	10–15 years	15–20 years	$P_{5-10\ vs.\ 10-15}$	$P_{5-10\ vs.\ 15-20}$	$P_{10-15\ vs.\ 15-20}$
<i>n</i>	74,677	39,414	35,263		9,341	21,168	44,168			
SBP (mmHg)	120 (110–128.5)	120.5 (111.5–130)	118.5 (110–126)		106 (100–112)	115 (109–122)	124 (117.5–132)			
DBP (mmHg)	70 (64–76)	70 (64–75.5)	70 (65–77)		63 (59.5–68.5)	68 (62–73)	72 (67.5–79)			
AAP 2017	44.1	47.6	40.2	<0.0001	31.4	30.9	53.2	0.43	<0.0001	<0.0001
KIGGS	29.5	24.5	35.1	<0.0001	30.7	31.2	28.4	0.33	<0.0001	<0.0001
fourth report	26.5	23.3	30.0	<0.0001	19.7	22.4	29.9	<0.0001	<0.0001	<0.0001

Unless otherwise indicated, data are presented as median and lower–upper quartile (25–75th percentile) or as percentage of patients diagnosed as hypertensive. $P < 0.05$ is considered significant and $P < 0.0001$ highly significant (χ^2 test). Boldface values indicate significant differences. f, females; m, males.

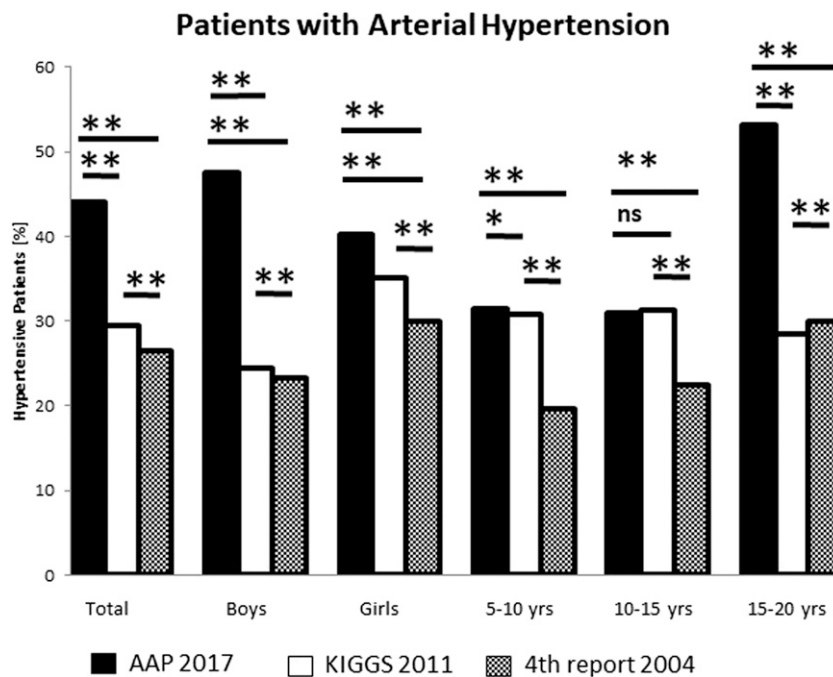


Figure 2—Rate of patients with HTN depending on the different references in the study population and the subgroups. * $P < 0.05$, ** $P < 0.0001$, not significant (ns), χ^2 test. yrs, years of age.

but lower based on the older reference values: AAP 2017 47.6% (boys) vs. 40.2% (girls), KiGGS 24.5% vs. 35.1%, fourth report 23.3% vs. 30.0%, respectively (all $P < 0.0001$, χ^2 test) (Table 2 and Fig. 2).

Age

The differences are strongly age dependent: there were only slight differences in the rate of HTN between AAP 2017 (31.4%) and KiGGS (30.7%) ($P = 0.003$, χ^2 test) in children <10 years of age. In the 10–14.9 year olds, 30.9% were hypertensive according to AAP 2017 and 31.2% according to KiGGS ($P = 0.08$). Prevalence of HTN was significantly lower using the reference values of the fourth report (5–9.9 years old, 19.6%, and 10–14.9 years old, 22.4%; all $P < 0.0001$, χ^2 test).

Of the teens >15 years old, 53.2% were diagnosed as hypertensive based on AAP 2017 compared with 28.4% (KiGGS) and 30.0% (fourth Report). HTN occurred less frequently by KiGGS than by fourth report (all $P < 0.0001$, χ^2 test) (Fig. 2).

Age and Sex

With application of the newer guidelines AAP 2017 and KiGGS, HTN prevalence was quite similar in the young children <10 years of age, whereas fourth report resulted in lower rates of HTN (all $P < 0.0001$, χ^2 test) (Fig. 3).

In the 10–15 year olds, AAP 2017 and KiGGS provided similar rates of HTN, both in girls and boys. Again, HTN prevalence was lowest based on fourth report (all $P < 0.0001$, χ^2 test) (Fig. 3).

For teenagers ≥ 15 years of age, HTN prevalence was significantly higher by AAP 2017 compared with KiGGS and fourth report and lower by KiGGS than by fourth report. These differences were greatest in boys (all $P < 0.0001$, χ^2 test) (Fig. 3).

Prevalence of HTN was higher in girls in most age-groups. HTN was slightly more frequent in boys 5–10 years of age with use of KiGGS and dramatically increased in teenage boys >15 years of age with use of AAP 2017 (Fig. 3).

Reclassification of Being Hypertensive

A total of 10,263 children with T1DM (13.7%) were identified as hypertensive by AAP 2017 but not by KiGGS and fourth report. These patients were older (median age 17.5 years), more often male (75%), taller (median height SDS 0.28), and had longer diabetes duration (median diabetes duration 6.5 years) compared with the total cohort, whereas HbA_{1c} levels (median 8.1%), BMI SDS (0.31), and insulin demand (0.87 units/kg body wt/day) were quite similar among the two groups (total cohort: 16.0 years, 52.8% male, 0.08, 5.3 years, 7.9%, 0.3, and 0.084 units/kg body wt/day, respectively) (Table 3).

CONCLUSIONS

Prevalence of HTN varied between 26.5% and 44.1% in our pediatric patients with T1DM, depending on reference values/guidelines. With use of the new AAP 2017 guideline, HTN increased from below 30% (KiGGS and fourth report) to 44.1% in the total cohort. BP regulation seems to be altered in almost every second child with T1DM, which resembles the rate of adult hypertensive patients in the U.S. and China (12). The prevalence found in our cohort is much higher than that in healthy children without diabetes, which is estimated at 2–4% (13), and other cohorts of children with T1DM (4–7%) (14,15). Previously, we also found lower rates for HTN in children with T1DM from Germany and Austria: 2008, 4%–13.9% (prepubertal children–adolescents, respectively) (16), and 2013, 20% (based on KiGGS and fourth report) (17). Within one decade, HTN prevalence seems to have more than doubled in pediatric patients documented in DPV. This might be attributed to different factors: firstly, in older investigations the cutoff for HTN was set at the 97th percentile and has meanwhile been lowered to the 95th percentile; secondly, the occurrence of overweight, obesity, or other risk factors for HTN might have increased in our children; and thirdly, a greater awareness of HTN has led to more regular and tighter BP monitoring in patients with T1DM.

However, all these observations are based on office BP only and not on ambulatory BP monitoring (ABPM). Therefore, white coat hypertension cannot be ruled out, which is reported to be present in up to 22% of the patients (18) and might play a role in the rise in office HTN over time. ABPM might also detect isolated nocturnal hypertension or masked hypertension; both have been identified as independent risk factors for CVD (19).

The increase in HTN attributed to use of 2017 AAP is strongly age dependent: in children <15 years of age, HTN differs only slightly between AAP 2017 and KiGGS, but in teens >15 years of age the implementation of AAP 2017 led to a significant increase of HTN prevalence: from $<30\%$ to 53.1%. From the age of 13 years onward, AAP 2017 uses adult cutoff levels of 130/80 mmHg to diagnose HTN, whereas KiGGS and fourth report stick to the 95th percentile up to an absolute cutoff level of 140/90 mmHg. In

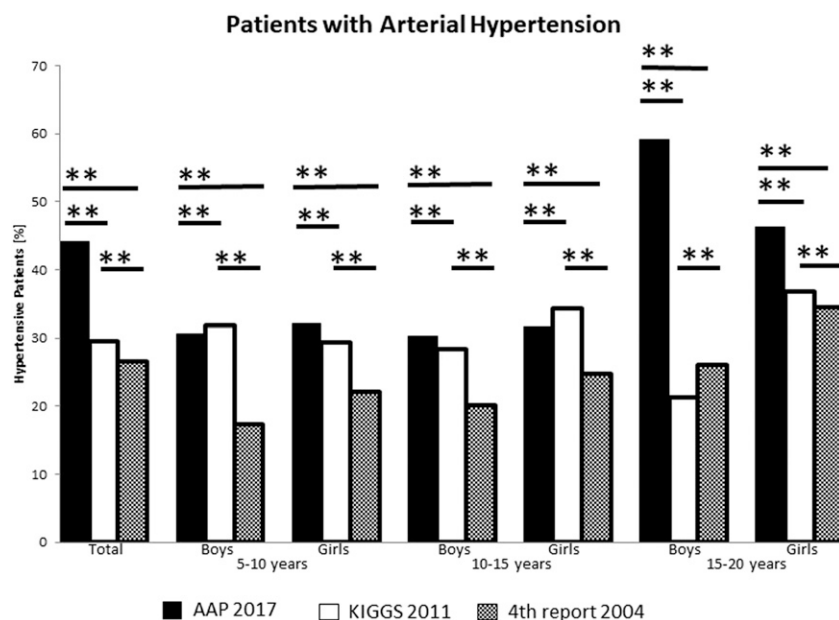


Figure 3—Rate of patients with HTN depending on the different references in the study population and the subgroups. $**P < 0.0001$, χ^2 test. years, years of age.

adolescents, the 95th percentile can reach absolute BP values $>130/90$ mmHg and, therefore, patients might be classified as nonhypertensive by KIGGS and fourth report but as hypertensive by AAP 2017. In our patients, this upward reclassification particularly affects teenage boys >15 years of age.

AAP 2017 and 2011 KIGGS BP references are based on normal weight children to exclude the influence of overweight and obesity, whereas the references of the fourth report are strictly population based and include overweight children as well. The 90th and 95th percentiles for BP are found to be 2–6 mmHg lower in KIGGS than in fourth report (10) and might explain the lower prevalence of HTN with use of the fourth report references, as children with T1DM tend to be overweight (BMI SDS 0.27). However, the increase of HTN within the last decade cannot be attributed to an increase of obesity, as the rates of overweight (11.3% vs. 10%) and obesity (5.3% vs. 3%) remained stable from 2003 (20) to 2015 (21) among children with T1DM in Germany and Austria.

Children with T1DM in the U.K.-based Clinical Practice Research Datalink (CPRD) aged >10 years had a higher risk of HTN than younger children (22), and thus teenage children, particularly with T1DM, are identified as a population at high risk for HTN.

In the total cohort, HTN is more frequent in boys than in girls. This sex gap is quite small among younger children, <15 years of age, and BP is even more often elevated in younger girls. The more recent guidelines, AAP 2017 and KIGGS (2011), showed similar HTN prevalence in younger children <15 years of age. Based on fourth report, prevalence of HTN was higher in girls for all age-groups, again hinting at overweight as the possible cause, as BMI SDS is higher in girls with T1DM.

Prevalence of HTN skyrockets up to nearly 60% in teenage boys ≥ 15 years of age if AAP 2017 is used but remains lower in boys than in girls based on KIGGS and fourth report. Teenage girls >15 years were also far more often classified as hypertensive by AAP2017. This implies that BP levels of teenage patients, particularly boys, must fall between the cutoffs of AAP 2017 (130/80 mmHg) and KIGGS/fourth report (95th percentile up to the absolute BP of 140/90 mmHg). In the KIGGS cohort of healthy German boys and girls, BP rises similarly in both sexes until the age of 13 years. But the pubertal rise in BP is significantly more pronounced in boys, resulting in BP differences of up to 17 mmHg for SBP and 2 mmHg for DBP between boys and girls (9). The significant increase of HTN in German teenage boys >13 years seems to be primarily independent of diabetes. On the other hand, T1DM per se enhances

the risk for arterial HTN, and chronic hyperglycemia is associated with HTN and cardiovascular disease. Thus, the massive increase of HTN in teenage boys documented in DPV with application of AAP 2017 seems to result from both diabetes and factors not related to diabetes.

Sharma et al. (23) studied the consequences of the new AAP 2017 on the prevalence and severity of elevated BP in healthy U.S. children from the National Health and Nutrition Examination Surveys (NHANES): children reclassified as hypertensive were more likely to be male and slightly taller than normotensive children. Our patients, whose BP was reclassified as hypertension by AAP 2017, were also more often male (75%) and taller (height SDS 0.28).

AAP 2017 is very sensitive to detect early alterations in BP regulation in T1DM and, therefore, classifies BP as hypertension earlier than KIGGS or fourth report, particularly in the teenage boys >15 years of age with T1DM documented in DPV.

Although it was not the original intent of our study, we found that the data reveal that 93.5% of the patients documented in DPV are not receiving antihypertensive medication. Based on the KIGGS references, office BP is increased in 29.5% and based on AAP 2017, 44.1%, but only 6.5% of the patients are on antihypertensive medication. There is an ongoing discussion among German pediatric diabetologists as to how to diagnose HTN in children with T1DM and when and how to treat. Thus far, there is a consensus that HTN should not be diagnosed based on a single office BP measurement, but BP >90 th percentile (KIGGS) measured repeatedly at two to three different visits should prompt further investigations—mainly ABPM. The awareness of the devastating consequences of HTN in T1DM needs to be sharpened among the German pediatric diabetologists and likely among pediatric diabetologists in other countries as well.

Children with T1DM are identified to have increased risk for HTN and diabetes complications resulting from HTN (1). Thus, AAP 2017 recommends regular monitoring of office BP; routine performance of ABPM should be strongly considered to assess HTN severity and determine whether abnormal circadian patterns are present, which may indicate increased risk for target organ damage (1). This risk might be reduced if elevated BP during

Table 3—Absolute BP and prevalence of arterial HTN and risk factors in the study population and the age-groups depending on sex

	5–10 years				10–15 years				15–20 years	
	Total	Boys	Girls	<i>P</i>	Boys	Girls	<i>P</i>	Boys	Girls	<i>P</i>
<i>n</i>	74,677	4,755	4,586		11,019	10,149		23,640	20,528	
SBP (mmHg)	120 110–128.5	106 100–112	106 100–112	0.46	115 109–122	115 109–122	0.35	126.5 120–134	121 115–129	<0.0001
DBP (mmHg)	70 64–76	63 59.5–68	63.5 60–69	0.01	68 62–72.5	69 62.5–74	<0.0001	72 67–78	73 68–79.5	<0.0001
AAP 2017 (%)	44.1	30.6	32.2	0.12	30.33	31.5	0.06	59.1	46.3	<0.0001
KIGGS (%)	29.5	31.9	29.4	0.01	28.4	34.3	<0.0001	21.1	36.7	<0.0001
fourth report (%)	26.5	17.3	22.1	<0.0001	20.2	24.7	<0.0001	26.0	34.4	<0.0001
BMI SDS	0.30 –0.3 to 0.4	0.27 –0.3 to 0.9	0.29 –0.3 to 0.9	0.61	0.11 –0.5 to 0.8	0.30 –0.3 to 0.9	<0.0001	0.18 –0.4 to 0.8	0.57 –0.5 to 1.1	<0.0001
Height SDS	0.8 –0.6 to 0.8	0.17 –0.5 to 0.9	0.17 –0.5 to 0.9	0.98	0.17 –0.5 to 0.8	0.12 –0.6 to 0.8	0.0002	–0.01 –0.7 to 0.7	0.05 –0.6 to 0.8	<0.0001
Insulin dosage (units/kg body wt/day)	0.84 0.7–1.0	0.67 0.5–0.8	0.7 0.6–0.9	<0.0001	0.83 0.7–1.1	0.87 0.7–1.1	<0.0001	0.89 0.7–1.1	0.86 0.7–1.1	<0.0001

Unless otherwise indicated, data are presented as median and lower–upper quartile (25–75th percentile) or as percentage of patients diagnosed as hypertensive. *P* < 0.05 is considered significant and *P* < 0.0001 highly significant (X² test). Boldface values indicate significant differences.

childhood were to resolve by adulthood (24).

The intention of the new 2017 AAP is to enhance the awareness of HTN in children and adolescents and to identify individuals at risk for HTN (25). It is the primary goal not to start antihypertensive medication in every child with high BP values right away but, rather, to identify children at risk for HTN, to initiate early diagnosis, and to start intervention if the diagnosis is confirmed, preferably by ABPM.

Conclusion

The identification of BP values as normo- or hypertensive strongly depends on the references applied. AAP 2017 results in a dramatic increase of HTN prevalence in older adolescents with T1DM, particularly in teenage boys. The implementation of AAP 2017 enhances the awareness of HTN and should prompt further evaluation. It should not result in immediate antihypertensive medication before confirmation of the diagnosis of HTN.

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