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Impact of Pubertal Development on Endothelial Function and Arterial Elasticity

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Abstract

Objectives—Little is known about the relation of pubertal development on endothelial function and arterial elasticity in children and adolescents; therefore, we compared brachial artery flow-mediated dilation (FMD) and carotid artery elasticity across Tanner (pubertal) stages in children and adolescents.

Study design—Blood pressure, fasting lipids, glucose, and insulin, body fat, insulin sensitivity (Mlbm), brachial FMD (percent dilation and area-under-the-curve), endothelium-independent dilation (EID peak dilation and area-under-the-curve), and carotid artery elasticity were evaluated across pubertal stages (Tanner I vs. Tanner II-IV vs. Tanner V) in 344 children and adolescents (184 males, 160 females; ages 6 to 21 years).

Results—124 subjects (mean age 8.23±0.15 years; 52 females) were Tanner stage I; 105 subjects (mean age 13.19±0.17 years; 47 females) were Tanner stages II–IV; and 115 subjects (mean age 17.19±0.16 years; 61 females) were Tanner stage V. There were no significant differences for any of the measures of vascular structure and function across pubertal stages.

Conclusion—Results of the current study indicate smooth muscle and endothelial function, as well as carotid artery elasticity, do not differ throughout pubertal development and that accounting for pubertal stage when reporting vascular data in children and adolescents may be unnecessary.

Keywords

Vasculature; Endothelium; Dilation; Children; Tanner Stage

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Throughout puberty, transient changes in cardiometabolic risk factors occur as a normal part of development. The relationship between puberty and cardiometabolic factors, such as body fatness, body mass index (BMI), lipids, and insulin resistance have been well documented.^{1–13} Specifically, increased insulin resistance is often associated with pubertal onset, with levels returning to near pre-pubertal status following maturation.⁹ Although insulin resistance is associated with adiposity throughout childhood and adolescence,^{9,11} differences in body fatness do not entirely explain the development of insulin resistance during puberty.^{7,9,11} It is possible that insulin resistance influences vascular health during pubertal development in children and adolescents.

A number of studies among children and adolescents have reported that endothelial function, as measured by flow-mediated dilation (FMD), is associated with obesity,¹⁴ dyslipidemia,¹⁵ blood pressure,¹⁶ insulin resistance,^{14,17} and oxidative stress.¹⁵ Studies also have measured arterial elasticity among children and adolescents.^{18,19} Among adults, BMI and elements of metabolic syndrome have been reported to have an inverse relationship with large and small artery compliance.^{20,21} Although it has been well-documented that cardiovascular and metabolic risk factors differ by pubertal stage, to our knowledge, no studies have examined whether measures of vascular function and stiffness differ across pubertal stages among children and adolescents. Therefore, the purpose of this study was to evaluate the association of Tanner stage and endothelial function and arterial elasticity among children and adolescents. We hypothesized that vascular variables would differ by pubertal stage in accordance with associated changes in cardiometabolic risk factors. Specifically, we hypothesized that FMD and arterial elasticity would be lowest among Tanner stages II–V compared with Tanner stages I and V.

METHODS

The study protocol was approved by the University of Minnesota Institutional Review Board. The study procedures adhered to the University of Minnesota's IRB and the Health Insurance Portability and Accountability Act guidelines. All parents and subjects provided informed consent and assent, respectively, for study participation.

Three hundred and forty-four subjects (184 males, 160 females), who had participated in a study evaluating cardiovascular risk among families, were included in this cross-sectional study. Enrolled children and adolescents were between the ages of 6 and 21 years of age (mean age 12.7 ± 4.1 years). Subjects had been fasting for at least eight hours prior to the vascular assessment and were asked to abstain from caffeine ingestion on the morning of testing and to avoid strenuous exercise or physical activity for 24 hours prior to the study visit. Subjects who were greater than 18 years of age were excluded from BMI-percentile, SBP-percentile, and DBP-percentile calculations.

Measurements for height and weight were obtained with a standard stadiometer (Ayrton, Model S100, Prior Lake, MN, USA) and electronic scale (ST Scale-Tronix, Serial No. 5002–8893, White Plains, NY, USA), respectively. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters-squared. Body composition was obtained using dual energy X-ray absorptiometry (DXA) (Lunar Prodigy, Software version 10.5, GE Healthcare Lunar, Madison, WI, USA). Blood pressure percentile data was classified based on The National Heart, Lung, and Blood Institute (NHLBI) guidelines.

Seated blood pressure was measured by a random-zero sphygmomanometer in the right arm, and the average of two systolic blood pressure (SBP) measurements and fifth phase Korotkoff diastolic blood pressure (DBP) measurements were analyzed. Tanner staging of pubertal development was performed by trained providers and was based on breast and

pubic hair development in girls and pubic hair development in boys. Participants were classified as pre-pubertal (Tanner I), pubertal (Tanner II–IV) and post-pubertal (Tanner V).

Insulin sensitivity, adjusted for lean body mass (Mlbm), was determined by euglycemic hyperinsulinemic clamp as previously described.¹¹ Fasting blood samples were obtained for serum insulin and lipids, as well as plasma glucose. Insulin levels were determined using a chemoluminescence immunoassay (Immulin Insulin DPC, Los Angeles, CA). Samples for serum lipids were analyzed with standard procedures at the Fairview-University Medical Center clinical laboratory.

Testing was performed in the Vascular Biology Laboratory in the University of Minnesota Clinical and Translational Science Institute. All the vascular studies were performed in a quiet, temperature-controlled environment (22–23°C). Vascular images were measured by a non-invasive ultrasound with subjects in the supine position. Images were digitized and stored on a personal computer for later off-line analysis with an electronic wall-tracking software program (Vascular Research Tools 5, Medical Imaging Application, LLC, Iowa City, IA, USA).

Following 15 minutes of quiet rest in the supine position, vascular images of the brachial artery were obtained using a conventional ultrasound scanner (Acuson, Sequoia 512, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA) with a 7.5 MHz linear array probe held at a constant distance from the skin and at a fixed point over the imaged artery. Assessment of FMD was performed by imaging the left brachial artery at the distal third of the upper arm using techniques previously described.^{22,23} After a 15-minute break following FMD assessment, endothelium-independent dilation (EID) was assessed using 0.3 mg sublingual nitroglycerin (NTG), the dose considered appropriate by the University of Minnesota Institutional Review Board for subjects <18 years old, and 0.4 mg sublingual NTG for subjects 18+ years old. Brachial artery diameter was assessed continuously for 5 minutes post-NTG administration. Peak dilation during the study was defined as the greatest percent change from resting brachial artery diameter, and area under the curve (AUC) was defined as the total relaxation of the brachial artery from resting baseline following reactive hyperemia or sublingual nitroglycerin administration.

Carotid artery images, as well as supine systolic and diastolic blood pressure and pulse pressure, were concurrently measured by a non-invasive ultrasound with subjects in the supine position. Following 15-min of quiet rest in the supine position, luminal systolic and diastolic diameters were obtained at a fixed point over the left common carotid artery, approximately 1 centimeter proximal from the carotid bulb. Images were collected at 20 frames per second for 10 seconds (200 frames) to ensure the capture of full arterial diameter change during a cardiac cycle. Systolic and diastolic blood pressures were recorded with an automated blood pressure sphygmomanometer during the 10-second carotid measurement. The mean diameter through the 10-second cycle was used to calculate measures of compliance and distensibility. The ultrasound scanning system was interfaced with a standard personal computer equipped with a data acquisition card for attainment of radio frequency ultrasound signals from the scanner. Digital image analysis was performed by the same trained reader blinded to group assignments.

Pulse pressure (P) was calculated as the difference between systolic and diastolic pressures. Additionally, maxDiamM denotes maximum diameter measurement, and minDiamM denotes minimum diameter measurement.

Statistical Analyses

SAS Software Package (Version 9.2, 2009, SAS Inc., Cary, NC, USA) was used for statistical analyses. Our study data were segmented into Tanner stages I, II–IV, and V groupings due to the equal-size, homogenous clusters within each stage of our study population. Results are expressed as mean±standard deviation (SD), unless otherwise stated. A one-way analysis of variance (ANOVA) was used to compare demographic characteristics by pubertal stage groups, as well as to compare vascular measures between-groups of pubertal stage groups, adjusting for age, sex, race, and baseline brachial artery diameter. An alpha value of 0.05 was used to signify statistical significance.

RESULTS

Tanner stage I included 124 children (mean age 8.23±0.15 years; 52 females); Tanner stages II–IV included 105 children and adolescents (mean age 13.19±0.17 years; 47 females); and Tanner stage V included 115 adolescents (mean age 17.19±0.16 years; 61 females).

Table I shows the descriptive and clinical characteristics of the three pubertal groups. Percent body fat and systolic blood pressure were significantly ($P<0.001$) lower among Tanner stage I, and diastolic blood pressure was significantly ($P<0.002$) higher among Tanner stage V. SBP-percentile ($P=0.48$) was not significantly different among the groups. DBP-percentile was significantly ($P=0.003$) lower in Tanner I than in Tanner II–IV; however, no significant difference was observed between Tanner II–IV and Tanner V. Fasting glucose and insulin were significantly different among the groups, with Tanner stage I having significantly ($P<0.0001$) lower fasting glucose and insulin levels than both Tanner stages II–IV and Tanner stage V. Participants with Tanner stages II–IV and Tanner stage V trended towards being significantly ($P=0.095$) different, with those in Tanner stages II–IV having higher values. MIbm was significantly different between all groups, with Tanner stage I exhibiting the highest values, followed by Tanner stages II–IV, then Tanner stage V (all $P<0.05$). Total cholesterol and LDL-cholesterol were significantly ($P<0.05$) higher in the Tanner stage I group, and HDL-cholesterol was significantly ($P<0.005$) lower in the Tanner stage V group. Furthermore, triglycerides increased with pubertal progression, with those in Tanner stage V observed to be significantly ($P<0.0003$) higher than those in Tanner stage I. Overall, mean descriptive and clinical measurements were observed to be within normal reference ranges for children and adolescents.

Baseline brachial artery diameter significantly increased ($P=0.012$) with pubertal progression. Specifically, significant differences between Tanner I and Tanner II–IV ($P=0.014$), as well as Tanner II–IV and Tanner V ($P=0.028$) were observed. Vascular measures, following adjustments by age, sex, race, and resting diameter, revealed no significant differences by group for FMD ($P=0.68$), FMD-AUC ($P=0.91$), EID ($P=0.88$), EID-AUC ($P=0.92$), diameter distensibility (DD) ($P=0.66$), cross-sectional distensibility (CSD) ($P=0.66$), diameter compliance (DC) ($P=0.18$), or cross-sectional compliance (CSC) ($P=0.41$). These findings did not change with additional adjustment for BMI-percentile. A separate analysis was also performed with adjustments for age, sex, and race (excluding resting diameter), and overall conclusions were the same; moreover, FMD ($P=0.33$), FMD-AUC ($P=0.68$), EID ($P=0.46$), EID-AUC ($P=0.17$), DD ($P=0.86$), CSD ($P=0.86$), DC ($P=0.29$), and CSC ($P=0.36$) were not significantly different by pubertal stage.

A sex-stratified analysis was also performed with adjustments for age, race, baseline diameter, and both with and without adjustment for BMI-percentile, revealing no significant difference between the Tanner stage groups for male and female children and adolescents separately.

DISCUSSION

The findings of the current study indicate that adjusting for pubertal stage might not be necessary when reporting vascular data among children and adolescents. The vascular findings are consistent with previously reported studies,^{24,25} which have suggested that resting brachial artery diameter was higher in each respective pubertal stage group. However, this appeared to have no impact on endothelial function across groups. In contrast to our findings, however, Bhangoo et al reported that endothelial peripheral arterial tonometry (EndoPAT) index, a measure of small artery endothelial function, increased with pubertal progression (Tanner stage I to Tanner stages IV–V) and was significantly correlated with age in healthy children and adolescents.²⁶ The divergent findings may be explained by the inherent differences in the vascular beds evaluated (conduit versus small artery). Arterial dilation in the conduit arteries is mostly dependent on nitric oxide whereas multiple factors contribute to dilation in the small arteries. In addition, smooth muscle is much more abundant in the conduit arteries. Finally, it is also possible that the “one size fits all” finger probes used with the EndoPAT device assessment provide less accurate reactive hyperemic index values in younger children. Future research should investigate the differences in conduit versus small artery endothelial function across pubertal stages in healthy children and adolescents, as well as diseased populations.

A notable observation of the current study was the lack of difference in smooth muscle function (EID) throughout pubertal development. This finding is important because the use of NTG in children is controversial and the lack of difference in EID across the pubertal groups in this study suggests that evaluation of smooth muscle function in children may be unnecessary. Additionally, future studies looking at smooth muscle function in children may not need to account for pubertal development.

Although not statistically significant, the current study showed higher carotid artery compliance and endothelial function, specifically FMD and FMD-AUC, among the Tanner stage I group. It is unclear whether these differences are clinically meaningful; however, this should be considered in studies where pre-pubertal children are compared with pubertal children.

The Tanner staging method used within the present study has been the standard for assessing the degree of pubertal development for more than 30 years,^{27,28} and it is the method used in previous studies of insulin resistance during puberty.^{1,12,29,30} Inherent in this method is a discordance between pubic hair growth and breast development in girls.²⁷ We scored both pubic hair and breast development in girls and used the greater of the two values for statistical analysis so that pubertal maturation would not be underestimated. Although pubic hair staging in boys often corresponds with testicular volume, pubic hair staging is not always the most accurate measure of gonadal maturation. Nonetheless, exclusion of genital examination was found to improve patient compliance with the study protocol.

Strengths of the current study include a relatively large sample size, balanced Tanner stage groups and the use of the euglycemic, hyperinsulinemic clamp, the gold standard technique for measuring insulin sensitivity. The primary limitation of the study was its cross-sectional nature. A longitudinal design would be preferred in order to better address the temporal association of pubertal development and arterial health.

In summary, the results from this cross-sectional study indicate that neither vascular function nor arterial compliance differs across pubertal stages in children and adolescents even though cardiometabolic risk factor levels vary. Although it is important to report Tanner stage in studies involving children and adolescents, the current findings suggest that adjustments for pubertal stage might not be necessary when reporting vascular data among

children and adolescents. Future prospective longitudinal studies should assess whether transient changes in cardiometabolic risk factor levels during puberty influence vascular health to confirm the results of the current study.

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ABBREVIATIONS AND ACRONYMS

BMI	Body mass index
CSC	Cross-sectional compliance
CSD	Cross-sectional distensibility
DC	Diameter compliance
DD	Diameter distensibility
DXA	Dual energy X-ray absorptiometry
EID	Endothelium-independent dilation
EID-AUC	Endothelium-independent dilation area-under-the-curve
FMD	Flow-mediated dilation
FMD-AUC	Flow-mediated dilation area-under-the-curve
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
Mlbm	Insulin sensitivity (M) adjusted for lean body mass (lbm)
NTG	Nitroglycerin

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Table 1

Mean ($\pm$ SD) Demographic and Clinical Characteristics

	Tanner I (n=124)	Tanner II-IV (n=105)	Tanner V (n=115)	Overall P-value	Tanner I vs. II-IV	Tanner I vs. V	Tanner II-IV vs. V
Age, years	8.23(0.15)	13.19(0.17)	17.19(0.16)	<0.0001	<0.0001	<0.0001	<0.0001
Sex (Male), n (%)	58.1(4.5)	55.2(4.9)	46.9(4.7)	0.21	0.67	0.09	0.22
Race, n (%)							
White	77.4(3.9)	81.9(4.3)	48.7(4.1)	<0.0001	0.44	<0.0001	<0.0001
Black	16.9(3.6)	11.4(3.9)	35.7(3.7)	<0.0001	0.30	0.0003	<0.0001
Height, cm	133.4(0.88)	159.8(0.96)	169.7(0.92)	<0.0001	<0.0001	<0.0001	<0.0001
Weight, kg	31.3(1.4)	54.9(1.5)	73.6(1.4)	<0.0001	<0.0001	<0.0001	<0.0001
BMI-percentile [‡]	59.3(2.5)	65.7(2.7)	70.3(2.6)	0.011	0.08	0.003	0.23
Percent Body Fat, DXA, %	20.9(0.97)	26.0(1.0)	28.2(1.0)	<0.0001	0.0004	<0.0001	0.13
SBP, mmHg	100.2(0.89)	108.0(0.97)	110.5(0.92)	<0.0001	<0.0001	<0.0001	0.07
SBP-percentile [§]	47.4(2.4)	47.7(2.5)	43.3(3.1)	0.48	0.94	0.28	0.27
DBP, mmHg	56.9(0.69)	57.4(0.75)	60.7(0.72)	0.0002	0.59	0.0001	0.002
DBP-percentile [§]	40.3(1.9)	32.1(2.0)	29.8(2.5)	0.0008	0.003	0.0007	0.27
Fasting Glucose, mg/dL	70.1(1.1)	86.7(1.1)	84.9(1.0)	<0.0001	<0.0001	<0.0001	0.23
Fasting Insulin, mU/L	4.0(0.62)	11.2(0.62)	9.78(0.59)	<0.0001	<0.0001	<0.0001	0.095
Mlbm, mg/kg lbm/min	15.8(0.74)	13.1(0.39)	11.8(0.38)	<0.0001	0.002	<0.0001	0.018
Total Cholesterol, mg/dL	156.0(2.6)	145.9(2.6)	147.3(2.5)	0.011	0.006	0.014	0.72
LDL-Cholesterol, mg/dL	91.0(2.1)	81.6(2.1)	84.6(2.1)	0.007	0.002	0.03	0.32
HDL-Cholesterol, mg/dL	52.3(1.1)	50.7(1.1)	46.4(1.0)	0.0003	0.28	0.0001	0.005
Triglycerides, mg/dL	63.3(3.9)	73.4(3.9)	83.5(3.8)	0.0014	0.08	0.0003	0.07

Standard Error of the Mean (SEM) used, unless otherwise noted. P-values <0.05 demonstrate significant differences between Tanner stages I, II-IV, and V. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Mlbm, insulin resistance (mg per kilogram of lean body mass); LDL, low-density lipoproteins; HDL, high-density lipoproteins.

[‡] Denotes Tanner group size (n=124, 105, 110).

[§] Denotes Tanner group size (n=123, 105, 72).

Table 2

LSmeans(SE) Vascular Response Measures

	Tanner I (n=124)	Tanner II-IV (n=105)	Tanner V (n=115)	Overall P-value	Tanner I vs. II-IV	Tanner I vs. V	Tanner II-IV vs. V
Baseline Diameter, mm	2.96(0.07)	3.17(0.04)	3.34(0.07)	0.012	0.014	0.003	0.028
FMD (%)	8.6(0.59)	7.96(0.37)	7.88(0.58)	0.68	0.39	0.52	0.90
FMD-AUC, %·s ⁻¹	805.4(74.5)	772.9(46.5)	786.1(73.5)	0.91	0.72	0.89	0.87
EID (%)	23.7(1.40)	24.4(0.67)	24.5(0.77)	0.88	0.61	0.67	0.91
EID-AUC, %·s ⁻¹	3870.3(264.8)	3768.7(126.1)	3758.0(141.1)	0.92	0.69	0.76	0.96
DD, %	14.5(0.59)	15.1(0.37)	15.4(0.58)	0.66	0.37	0.41	0.71
CSD, %	31.2(1.4)	32.7(0.85)	33.2(1.3)	0.66	0.37	0.42	0.71
DC, mm-mmHg ⁻¹	0.013(0.002)	0.018(0.001)	0.018(0.002)	0.18	0.06	0.17	0.81
CSC, mm ² -mmHg ⁻¹	0.18(0.008)	0.16(0.005)	0.16(0.008)	0.41	0.19	0.22	0.54

LSmeans(SE) adjusted for Age, Sex, Race, and Baseline Diameter. P-values <0.05 demonstrate significant differences among Tanner stages I, II-IV, and V. Baseline diameter (baseline brachial artery diameter at rest); FMD, flow-mediated dilation; FMD-AUC, flow-mediated dilation area-under-the-curve; EID, endothelium-independent dilation; EID-AUC, endothelium-independent dilation area-under-the-curve; DD, diameter distensibility; CSD, cross-sectional distensibility; DC, diameter compliance; CSC, cross-sectional compliance.