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ORIGINAL RESEARCH

Relationship of Circulating Endothelial Cells With Obesity and Cardiometabolic Risk Factors in Children and Adolescents

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BACKGROUND: Circulating endothelial cells (CECs) reflect early changes in endothelial health; however, the degree to which CEC number and activation is related to adiposity and cardiovascular risk factors in youth is not well described.

METHODS AND RESULTS: Youth in this study (N=271; aged 8–20 years) were classified into normal weight (body mass index [BMI] percentage <85th; n=114), obesity (BMI percentage ≥95th to <120% of the 95th; n=63), and severe obesity (BMI percentage ≥120% of the 95th; n=94) catagories. CEC enumeration was determined using immunohistochemical examination of buffy coat smears and activated CEC (percentage of vascular cell adhesion molecule-1 expression) was assessed using immunofluorescent staining. Cardiovascular risk factors included measures of body composition, blood pressure, glucose, insulin, lipid profile, C-reactive protein, leptin, adiponectin, oxidized low-density lipoprotein cholesterol, carotid artery intima–media thickness, and pulse wave velocity. Linear regression models examined associations between CEC number and activation with BMI and cardiovascular risk factors. CEC number did not differ among BMI classes (P>0.05). Youth with severe obesity had a higher degree of CEC activation compared with normal weight youth (8.3%; 95% CI, 1.1–15.6 [P=0.024]). Higher CEC number was associated with greater body fat percentage (0.02 per percentage; 95% CI, 0.00–0.03 [P=0.020]) and systolic blood pressure percentile (0.01 per percentage; 95% CI, 0.00–0.01 [P=0.035]). Higher degree of CEC activation was associated with greater visceral adipose tissue (5.7% per kg; 95% CI, 0.4–10.9 [P=0.034]) and non–high-density lipoprotein cholesterol (0.11% per mg/dL; 95% CI, 0.01–0.21 [P=0.039]).

CONCLUSIONS: Methods of CEC quantification are associated with adiposity and cardiometabolic risk factors and may potentially reflect accelerated atherosclerosis as early as childhood.

Key Words: adolescents ■ cardiovascular risk ■ children ■ endothelial health ■ novel biomarkers ■ obesity

The prevalence of obesity among US youth stands at ≈18%, and, in recent years, there has been a precipitous increase in severe obesity among children and adolescents.[1] Obesity in childhood increases the risk for premature cardiovascular disease (CVD) morbidity[2–4] and mortality.[5] While overt CVD (eg, myocardial infarction and stroke) typically does not occur until adulthood, endothelial dysfunction, one of the earliest hallmarks of atherosclerosis, is detectable in childhood and predictive of future cardiac events.[6,7] However, assessing endothelial health in youth remains a challenge because of methodological limitations. Gold-standard measures of endothelial health require invasive procedures, specialized equipment, and highly trained technicians, and the majority of these techniques are not widely applicable in clinical settings.[8,9]

Whole blood circulating endothelial cells (CECs) are thought to reflect vascular activation and damage based on research in adults, yet they may have a

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CLINICAL PERSPECTIVE

What Is New?

- Circulating endothelial cells (CECs) are noninvasive biomarkers of endothelial health that have not been extensively studied in youth.
- We found that CEC activation was elevated in youth with severe obesity and was associated with visceral adiposity and high-density lipoprotein cholesterol, whereas CEC number was associated with higher body fat and systolic blood pressure.
- Methods of CEC quantification are differentially associated with adiposity and cardiometabolic risk factors in youth.

What Are the Clinical Implications?

- These findings indicate that youth with severe obesity may express early signs of vascular activation, highlighting the need to intervene early with effective prevention strategies.
- While more research is needed to understand the role of CEC in the pathology of cardiovascular disease, methods of CEC quantification continue to show promise as a useful biomarker of endothelial health in youth.

Nonstandard Abbreviations and Acronyms

CEC	circulating endothelial cell
VCAM-1	vascular cell adhesion molecule expression-1

role as a noninvasive biomarker of endothelial health as early as childhood. Higher numbers of CECs may represent more advanced structural damage to the endothelium, while increased vascular cell adhesion molecule-1 (VCAM-1) on the cell surface is reflective of CEC activation.[10–12]

While a relationship between CEC and cardiometabolic health has been established in adults,[12–16] CECs have not been extensively investigated as a disease risk biomarker in youth. Recently, we established the reproducibility and reliability of circulating CECs in a pediatric population.[17] Given that CECs are directly representative of endothelial cell distress, they may be especially useful for identifying high-risk individuals and may have potential for use as risk-prediction biomarkers.[18] Our primary objective was to examine CEC enumeration and activation among body mass index (BMI) classes in children and adolescents. The secondary aim of this study was to examine the association of CEC number and degree of activation with measures of adiposity, cardiometabolic risk factors, and vascular health.

METHODS

The data supporting the findings of this study are available from the corresponding author on reasonable request.

Study Design and Participants

This cross-sectional study[19] included children and adolescents aged between 8 and 20 years with normal weight (BMI <85th percentile; n=114), obesity (BMI ≥95th percentile to <120% of the 95th percentile; n=63), and severe obesity (BMI ≥120% of the 95th percentile; n=94) based on Centers for Disease Control and Prevention (CDC)–defined age- and sex-specific BMI percentiles.[20,21] Normal-weight youth were recruited from a network of general pediatric care clinics in the greater Minneapolis and St. Paul metropolitan area and by advertisement. Youth with obesity and severe obesity were primarily recruited from the University of Minnesota Pediatric Weight Management Clinic. Exclusion criteria included the following: (1) obstructive sleep apnea, (2) obesity from a known genetic cause, (3) history of metabolic/bariatric surgery, (4) use of current medications known to affect endothelial health, and (5) injury or diagnoses of chronic conditions (eg, obstructive sleep apnea and diabetes mellitus) that may influence endothelial health. The protocol was approved by the University of Minnesota's institutional review board and consent and assent were obtained from parents/guardians and participants, respectively, before any study procedures.

Anthropometrics, Body Fat, and Cardiometabolic Risk Factors

All testing occurred in the morning after an 8-hour fast at the University of Minnesota Clinical and Translational Science Institute. Height and weight were assessed using a wall-mounted stadiometer and electronic scale, respectively. BMI was calculated as body weight in kilograms divided by height in meters squared. Body composition was measured by dual x-ray absorptiometry (iDXA; GE Healthcare) and analyzed using enCore version 16.2 (GE Healthcare). Visceral adipose tissue was estimated using CoreScan (GE Healthcare) as previously described.[22–24] A trained physician or registered nurse performed Tanner staging to assess pubertal maturation. After a period of rest, seated blood pressure (BP) was measured 3 times consecutively and

the average of the last 2 measures were reported for systolic BP and diastolic BP. Fasting lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol [HDL-C], and triglycerides), glucose, and insulin were measured and analyzed using standard procedures at the Fairview diagnostics Laboratories at the Fairview-University Medical Center (Minneapolis, MN), a CDC-certified laboratory. C-reactive protein, leptin, adiponectin, and oxidized low-density lipoprotein cholesterol were assayed with multiplex in the University of Minnesota Cytokine Reference Laboratory.

CEC Number and Activation

Analyses of CECs were performed within 3 hours of the blood draw in the University of Minnesota Vascular Biology Center. Details on CEC analysis have been previously published.[11,17,25] CEC enumeration was determined using immunohistochemical examination of buffy coat smears. CECs were stained with the antibody P1H12 (CD146). Secondary anti–mouse IgG antibody labeled with alkaline phosphatase was applied for 40 minutes. Cells positive for P1H12 (CEC) were visualized using alkaline phosphatase Fast Red substrate (Vector Laboratories) and the nuclei of cells were counterstained with hematoxylin staining. CECs on the smear were manually counted under a light microscope. The results were expressed as the number of CEC per 1 mL of peripheral whole blood.

Activated CECs (%VCAM-1 expression) were assessed using immunoflourescent staining. Activated CEC were determined using immunomagnetic beads from Dynal, m-450, coated with anti–mouse IgG and incubated with P1H12 antibody. The beads with CECs attached were spun down using cytospin centrifuge. The panel of antibodies used for double staining included mouse P1H12 (endothelial marker), rabbit anti–VCAM-1 (Santa Cruz Biotechnology), anti–mouse fluorescein isothiocyanate labeled, and anti–rabbit TRITC labeled (both from Jackson IRL). Nuclei were counterstained using DAPI. Slides were viewed under a fluorescent microscope and the results were expressed as a %VCAM-1–positive CEC among the total population of CECs.[11]

Measures of Vascular Health

A trained sonographer performed vascular testing in the Vascular Biology Laboratory in a quiet, temperature-controlled environment (22°C–23°C). Carotid intima–media thickness was measured using a conventional ultrasound scanner (Acuson, Sequoia 512; Siemens Medical Solutions USA, Inc.) with a 15-8 MHz linear array probe. B-mode images of the far wall of the right and left common carotid artery, carotid bulb, and internal carotid artery were obtained at end diastole (gated by R wave on ECG). All images were digitized and analyzed using electronic wall-tracking software (Vascular Research Tools 5; Medical Imaging Application, LLC). Right radial and carotid artery waveforms, as well as carotidradial pulse wave velocity, were recorded by applanation tonometry using SphygmoCor MM3 version 8.0 software (AtCor Medical). Radial and carotid artery augmentation index, both corrected to a heart rate of 75 beats per minute, were derived from a validated integral transfer function applied by SphygmoCor MM3. Pulse wave velocity was measured by the sequential acquisition of pressure waveforms from the carotid and radial artery using the same tonometer. Carotid-radial pulse wave velocity was calculated from the transit time between the 2 arteries relative to the R wave within the ECG complex using the foot-to-foot method and the intersecting tangent algorithm.[26–28]

Statistical Analysis

Descriptive statistics included mean and SD for continuous variables and frequency with percentage for categorical variables. Linear regression models were used to compare CEC enumeration and activation among BMI groups, adjusting for Tanner stage, sex, and race/ethnicity with robust variance estimation for CIs and *P* values. Additional linear models were used to evaluate the associations between cardiometabolic risk factors and measures of vascular health with CEC enumeration and activation after controlling for the same covariates. All analyses were conducted using R version 3.5.3 (R Core Team).

RESULTS

Youth with severe obesity tended to be more advanced in pubertal status and were more likely to be female compared with those in other BMI classes. Youth with obesity and severe obesity tended to have higher levels of adiposity and cardiometabolic risk factors, including higher BP, lipids, and insulin (Table 1). Youth with obesity and severe obesity also displayed more adverse markers of vascular health compared with normal weight youth, including higher levels of C-reactive protein, leptin ratio, and oxidized low-density lipoprotein. The measures of vascular health, carotid intima–media thickness, and pulse wave velocity were comparable between BMI classes. CEC number and degree of activation (%VCAM-1 expression) increased among BMI classes, from normal weight to severe obesity.

Regarding CEC number, there was no statistically significant difference between the obesity group and normal-weight group or the severe obesity group and the normal-weight group, after adjusting for Tanner stage, sex, race, and ethnicity (both $P>0.050$; Table 2). Youth with severe obesity had a significantly higher

Table 1. Demographic, Clinical, and Biomarker Characteristics

Covariate	Normal Weight n=114	Obesity n=63	Severe Obesity n=94
Male	64 (56.1%)	31 (49.2%)	37 (39.4%)
Age, y	12.7 (2.5)	12.3 (2.5)	13.4 (3.0)
Race/Ethnicity			
Black	11 (9.6%)	4 (6.3%)	11 (11.7%)
White	95 (83.3%)	47 (74.6%)	66 (70.2%)
Other (including Asian, American Indian/Alaskan Native, multiple race)	8 (7.0%)	12 (19.0%)	17 (18.1%)
Latino/Hispanic	7 (6.1%)	10 (15.9%)	18 (19.1%)
Tanner stage			
I	42 (36.8%)	21 (33.3%)	12 (12.8%)
II	19 (16.7%)	13 (20.6%)	21 (22.3%)
III	20 (17.5%)	12 (19.0%)	18 (19.1%)
IV	22 (19.3%)	10 (15.9%)	24 (25.5%)
V	11 (9.6%)	7 (11.1%)	19 (20.2%)
Weight, kg	45.1 (12.9)	67.5 (17.4)	97.3 (27.5)
Height, cm	154 (14.3)	155 (13.9)	162 (12.5)
Body mass index, kg/m^2	18.5 (2.42)	27.4 (3.21)	36.5 (6.32)
Percent body fat, %	25.0 (5.97)	41.7 (5.59)	48.3 (4.99)
Visceral adipose tissue, kg	0.08 (0.05)	0.48 (0.26)	1.13 (0.62)
DBP (percentile)	31.4 (20.0)	36.8 (22.2)	42.9 (24.1)
SBP, mm Hg	106 (9.73)	114 (11.0)	122 (12.2)
LDL-C, mg/dL	81 (24)	95 (22)	96 (26)
HDL-C, mg/dL	59 (13)	46 (11)	40 (9)
Non-HDL-C, mg/dL	95 (27)	118 (29)	123 (29)
Total cholesterol, mg/dL	154 (27)	164 (26)	163 (31)
Triglyceride/HDL-C ratio	1.32 (0.65)	2.89 (1.99)	3.6 (1.86)
Glucose, mg/dL	77.5 (9.1)	80.7 (8.3)	79.9 (7.8)
Insulin, mU/L	4.3 (2.9)	10.3 (5.9)	17.3 (11.0)
Carotid intima–media thickness, mm	0.53 (0.04)	0.51 (0.07)	0.48 (0.09)
Pulse wave velocity, m/s	6.73 (1.14)	6.61 (1.18)	6.58 (1.11)
C-reactive protein, mg/L	1.54 (3.3)	7.66 (11.4)	8.59 (8.58)
Leptin ratio	0.26 (0.42)	1.64 (2.03)	3.61 (3.54)
Oxidized LDL-C, U/L	42.1 (21.2)	57.6 (37.2)	65.0 (39.5)
HMW adiponectin, µg/mL	5.44 (3.63)	3.37 (2.06)	2.43 (1.57)
CEC outcomes			
CEC number (count of cells per mL of whole blood)	0.72 (1.21)	0.78 (1.11)	1.15 (2.18)
CEC number (categorical by count of cells per mL of whole blood)			
0	71 (62.3%)	33 (52.4%)	53 (56.4%)
1	22 (19.3%)	19 (30.2%)	16 (17.0%)
2	12 (10.5%)	7 (11.1%)	14 (14.9%)
3	4 (3.5%)	2 (3.2%)	3 (3.2%)
4	2 (1.8%)	0 (0.0%)	2 (2.1%)
≥5	3 (2.6%)	2 (3.2%)	6 (6.4%)
CEC activation (%VCAM-1 expression)	53.4 (27.5)	54.4 (25.8)	61.5 (25.1)

Data are expressed as mean (SD) or number (percentage).

CEC indicates circulating endothelial cell; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HMW , high-molecular-weight; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; and VCAM-1, vascular cell adhesion molecule expression-1.

Table 2. Linear Model Comparing Mean CEC Number Among BMI Classes, Adjusting for Tanner Stage, Sex, Race, and Ethnicity

Covariate	Mean Difference in CECs (95% CI)	*P* Value
BMI group		
Normal	Reference	…
Obesity	0.04 (−0.31 to 0.40)	0.808
Severe obesity	0.35 (−0.14 to 0.84)	0.158
Sex		
Male (vs female)	−0.16 (−0.51 to 0.19)	0.364
Tanner stage		
I	Reference	…
II, III, IV	0.36 (0.03 to 0.70)	0.033
V	0.51 (−0.20 to 1.22)	0.156
Race		
White	Reference	…
Black	−0.52 (−1.00 to −0.03)	0.036
Other (including Asian, American Indian/Alaskan Native, multiple race)	0.13 (−0.49 to 0.75)	0.690
Ethnicity		
Latino (vs not Latino)	−0.31 (−0.77 to 0.15)	0.183

BMI indicates body mass index; and CEC, circulating endothelial cell.

degree of CEC activation compared with those with normal weight (8.3%; 95% CI, 1.1–15.6 [*P*=0.024) (Table 3). Differences in CEC activation between youth with obesity and those with normal weight were not statistically significant (*P*=0.873).

Body fat percentage (0.02 per percentage; 95% CI, 0.00–0.03 [*P*=0.02]) was positively associated with CEC number after adjusting for Tanner stage, sex, race, and ethnicity (Table 4). No other measure of adiposity, cardiometabolic risk factor, or measure of vascular health was associated with CEC number. Given the known associations between BMI and cardiovascular health, additional linear models were conducted after adjusting for BMI. Results were similar in terms of associations among cardiometabolic risk factors, measures of vascular health, and CEC enumeration, after adjusting for BMI. Additional exploratory analyses examined differences in associations across Tanner stage by sex; however, no significant differences were observed.

Visceral adipose tissue (5.7% per kg; 95% CI, 0.4–10.9 [*P*=0.034]) and non–HDL-C (0.1% per mg/dL; 95% CI, 0.0–0.2 [*P*=0.039]) were positively associated with CEC activation after adjusting for Tanner stage, sex, race, and ethnicity (Table 5). However, after additionally adjusting for BMI, the relationship between non–HDL-C and CEC activation was no longer significant (*P*=0.776). No other measure of adiposity, cardiometabolic risk factor, or measure of vascular health was associated with CEC number. Exploratory analyses showed significant differences in the association

Table 3. Linear Model Comparing Mean CEC Activation (VCAM %) Among BMI Classes, Adjusting for Tanner Stage, Sex, Race, and Ethnicity

Covariate	Mean Difference in VCAM % (95% CI)	*P* Value
Sex		
Male (vs female)	3.2 (−3.2 to 9.5)	0.326
BMI group		
Normal	Reference	…
Obesity	0.7 (−7.3 to 8.6)	0.873
Severe obesity	8.3 (1.1 to 15.6)	0.024
Tanner stage		
I	Reference	…
II, III, IV	−4.9 (−12.2 to 2.5)	0.192
V	4.2 (−5.3 to 13.6)	0.391
Race		
White	Reference	…
Black	3.2 (−6.0 to 12.3)	0.499
Other (including Asian, American Indian/Alaskan Native, multiple race)	−4.1 (−14.2 to 6.0)	0.429
Ethnicity		
Latino (vs not Latino)	−3.6 (−13.5 to 6.4)	0.481

BMI indicates body mass index; CEC, circulating endothelial cell; and VCAM-1, vascular cell adhesion molecule expression-1.

Table 4. Multiple Linear Models to Examine Associations Among Each Cardiometabolic Risk Factor and Measure of Vascular Health With CEC Number, Adjusting for Tanner Stage, Sex, Race, and Ethnicity

Covariate	Mean Difference in CEC (95%CI)	*P* Value
Body fat, %	0.02 (0.00 to 0.03)	0.020
Visceral fat mass, kg	0.22 (−0.15 to 0.59)	0.235
SBP, %	0.01 (0.00 to 0.01)	0.035
Total cholesterol, mg/dL	0.00 (0.00 to 0.01)	0.273
LDL-C, mg/dL	0.00 (0.00 to 0.01)	0.211
HDL-C, mg/dL	−0.00 (−0.02 to 0.01)	0.652
Non–HDL-C, mg/dL	0.00 (0.00 to 0.01)	0.283
Trigylceride/HDL-C ratio	0.11 (−0.14 to 0.35)	0.402
Glucose, mg/dL	−0.01 (−0.03 to 0.02)	0.600
Insulin, mU/L	0.02 (−0.01 to 0.03)	0.135
C-reactive protein, mg/L	0.01 (−0.02 to 0.03)	0.486
Leptin ratio	0.06 (−0.05 to 0.17)	0.320
Oxidized LDL-C, U/L	0.01 (0.00 to 0.08)	0.131
HMW adiponectin, µg/mL	−0.04 (−0.10 to 0.03)	0.255
Carotid intima–media thickness, mm	−1.5 (−4.80 to 1.88)	0.392
Pulse wave velocity, m/s	0.04 (−0.12 to 0.20)	0.624

CEC indicates circulating endothelial cell; HDL-C, high-density lipoprotein cholesterol; HMW, high-molecular-weight; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

Table 5. Multiple Linear Model to Examine Associations Among Mean CEC Activation (VCAM %), Cardiometabolic Risk Factors and Measures of Vascular Health, Adjusting for Tanner Stage, Sex, Race, and Ethnicity

Covariate	Mean Difference in VCAM % (95%CI)	*P* Value
Body fat, %	0.2 (–0.1 to 0.5)	0.210
Visceral fat mass, kg	5.7 (0.4 to 10.9)	0.034
SBP, %	0.2 (0.0 to 0.2)	0.115
Total cholesterol, mg/dL	0.1 (0.0 to 0.2)	0.087
LDL-C, mg/dL	0.1 (0.0 to 0.2)	0.105
HDL-C, mg/dL	–0.1 (–0.4 to 0.1)	0.359
Non–HDL-C, mg/dL	0.1 (0.0 to 0.2)	0.039
Triglyceride/HDL-C ratio	2.1 (–0.9 to 5.0)	0.166
Glucose, mg/dL	0.3 (–0.1 to 0.6)	0.120
Insulin, mU/L	0.3 (–0.1 to 0.7)	0.159
C-reactive protein, mg/L	–0.1 (–0.4 to 0.2)	0.598
Leptin ratio	0.1 (–1.3 to 1.5)	0.883
Oxidized LDL-C, U/L	0.0 (–0.1 to 0.1)	0.956
HMW adiponectin, µg/mL	–0.3 (–1.5 to 0.9)	0.634
Carotid intima–media thickness, mm	–1.5 (–4.8 to 1.9)	0.392
Pulse wave velocity, m/s	–1.2 (–3.9 to 1.6)	0.402

CEC indicates circulating endothelial cell; HDL-C, high-density lipoprotein cholesterol; HMW, high-molecular-weight; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; and VCAM-1, vascular cell adhesion molecule expression-1.

between non–HDL-C and CEC activation by sex (*P*=0.033) and differences in the association between body fat percentage and CEC activation across Tanner stage (*P*=0.01).

DISCUSSION

To our knowledge this is the largest and most comprehensive study to examine the relationship of CEC number and degree of activation with obesity, cardiometabolic risk factors, and vascular health in the pediatric population. In order to improve understanding of the pathophysiology and clinical management of cardiovascular disease, particularly in the context of obesity, novel biomarkers of early atherosclerosis must be evaluated and validated in pediatric populations.[29,30] While we did not observe statistically significant differences in CEC number among BMI classes, degree of CEC activation was elevated in the context of severe obesity. CEC number was positively associated with total body fat and systolic BP. Degree of CEC activation was positively associated with visceral adipose tissue and non–HDL-C. Neither CEC number nor CEC activation were associated with any of the other cardiometabolic risk factors or measures of vascular health.

Our finding that CEC activation is elevated in pediatric severe obesity suggests that youth with severe obesity may express early signs of vascular activation, which may potentially place them at higher risk for developing accelerated atherosclerosis. Previous studies have reported that youth with severe obesity experience higher levels of vascular dysfunction and are at higher risk for CVD compared with youth with normal weight.[19,31–33] Findings in adults have demonstrated that elevated endothelial activation is associated with subsequent atherosclerosis and is predictive of future cardiac events.[34] Therefore, youth with higher levels of CEC activation may be at higher risk for future cardiac events; however, more research is needed to understand the role of CEC activation in the pathology of CVD across the lifespan and their ability to predict vascular disease in adulthood.[29]

CEC number was positively associated with body fat and systolic BP while degree of CEC activation was positively associated with higher levels of visceral adipose tissue and non–HDL-C. These findings suggest that adiposity, elevated BP, and/or dyslipidemia may be underlying mechanisms by which endothelial activation is increased in the context of pediatric obesity. Previous studies in youth have shown that hypertension and dyslipidemia trigger a disruption in vasoactive factors, leading to endothelial damage, especially in the context of higher levels of adiposity.[35]

Given that the endothelium is responsive to treatments such as lifestyle intervention[36] and pharmacotherapy,[37] there is a need for sensitive biomarkers to identify the early stages of endothelial dysfunction when prevention interventions are most effective.[37,38] Quantification of CEC activation continues to show promise as a useful biomarker in pediatric populations.[17,25] However, it is also important to note that differences in CEC number and degree of activation between youth with normal weight and those with moderate (ie, less than severe) obesity were not detected in this study. These findings may point to the complexity and diversity of factors, including genetic predispositions and environmental influences, that contribute to endothelial activation and the development of CVD.[33,39] Alternatively, CEC number and degree of activation may be markers of more extreme endothelial damage that only surfaces in the most severe forms of obesity where there has been greater and longer exposure to detrimental lifestyle factors. Given the complex interplay among CVD risk factors, CEC may have potential for use in a composite score of endothelial health that can be used to identify high-risk youth as is done in CVD risk prediction equations in adults. Previous studies have demonstrated that the clustering of ≥2 cardiovascular risk factors is associated with abnormal vascular structure and function in youth[40] and that clustering and composite CVD health scores are reliable tools in clinical practice.[41]

The strengths of this study include utilization of a cohort with a wide range of BMI values, ages, and stages of pubertal maturation. This study also included key cardiometabolic factors and measures of vascular health, allowing us to compare CECs with validated measures of endothelial health. Limitations include the fact that we did not control for genetic markers of CVD, lifestyle factors (ie, diet or physical activity), or sociodemographic factors that may influence endothelial cell biology.[42,43] Furthermore, our study is limited by its cross-sectional design and we did not adjust for multiple comparisons, which may have increased the odds of false-positive results. Longitudinal studies are needed to determine the role of CEC number and activation in the progression of CVD across the lifespan and their ability to predict downstream cardiac events in adulthood in order to evaluate their potential for use in the clinical treatment and management of CVD risk.[29]

CONCLUSIONS

CEC activation was significantly elevated in the context of severe obesity and was associated with excess visceral adiposity and non–HDL-C. Higher CEC number was not found to be significantly different among BMI groups, but was associated with higher total body fat and higher systolic BP percentile. These findings suggest that various methods of CEC quantification are differentially associated with adiposity and cardiometabolic risk factors in youth.

ARTICLE INFORMATION

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