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A Novel Approach to the Study of Pediatric Obesity: A Biomarker Model

Shari Barkin, MD, MSHS,

Marian Wright Edelman Professor of Pediatrics; Director of Division of General Pediatrics; and Director of Pediatric Obesity Research, Diabetes Research and Training Center at the Vanderbilt University School of Medicine, Nashville, TN

Yamini Rao, MD,

First-year resident in the Department of Pediatrics, University of California, San Francisco, CA

Padget Smith, BS, and

Medical student at the Carver College of Medicine, University of Iowa, Iowa City, IA

Eli Po'e, BS

Research Assistant II at Vanderbilt University Medical Center, Nashville, TN

Increases in sedentary lifestyle and high calorie food consumption, among other factors, have contributed to epidemic levels of childhood obesity in the United States.¹ Children who are overweight during the preschool period are more likely to become overweight adolescents and obese adults.² In fact, a rapid gain in body mass index (BMI) in early childhood has been shown to affect adulthood mortality and morbidity.³ Therefore, it appears that common forms of obesity often have their roots in childhood.

Yet, the biologic processes underpinning the connection between childhood and later adulthood obesity are unclear. The body attempts to maintain stability through change. It does this every minute of every day by maintaining narrow set points, such as body temperature through homeostasis, while more dynamically regulating large systems, such as the cardiovascular system (CVS); immune system; sympathetic nervous system (SNS); metabolic system; hypothalamic-pituitary-adrenal axis (HPA axis); and central nervous system (CNS). This concept is called “allostasis.”

Allostasis is a multifactorial biomarker model that captures the complex regulation and relationship between multiple systems.⁴ Whereas allostasis designates processes of bodily adaptation to stressful challenges, “allostatic load” (AL) refers to the wear and tear on the body as a consequence of dysfunctional allostasis. AL is a cumulative measure of dysregulation across multiple physiological systems, and it has been postulated to affect health risks and health outcomes.^{4,5}

Address correspondence to: Shari L. Barkin, MD, MSHS, Marian Wright Edelman Professor of Pediatrics; Director of Division of General Pediatrics; Director of Pediatric Obesity Research, Diabetes Research and Training Center, Vanderbilt University School of Medicine, 2200 Children's Way, Doctor's O'ce Tower 8232, Nashville, TN 37232-9225; fax: 615-936-1730; shari.barkin@vanderbilt.edu.

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More than a decade ago, Seeman and colleagues⁴ postulated the use of 10 biomarkers to comprise an AL composite score for adults (Table 1, see page 252). Since that time, adipose tissue has evolved as a major hormonal regulator that needs to be included in our consideration of how the body coordinates hormonal information. Therefore, the major coordinated systems in the development of AL include: 1) the SNS; 2) the HPA axis; 3) the metabolic response to energy expenditure (ie, metabolism); 4) the immune/inflammatory system; 5) the cardiovascular system (CVS); and 6) the adipose tissue.

Biomarkers related to each of these systems reflect different stages of disease processes. For example, primary mediators such as adiponectin have early effects at the cellular level, influence secondary outcomes such as cardiovascular disease (CVD), and finally manifest as tertiary outcomes such as diabetes.

The allostatic model could potentially provide a useful approach to further understanding childhood obesity. However, AL is a concept that has been applied predominantly to adults. We conducted a systematic literature review to 1) assess the use of this concept in pediatric populations related to childhood growth; and 2) identify potential biomarkers of AL associated with pediatric growth pattern trajectories.

METHODS

Literature Search Strategy

We conducted a systematic literature review, with eligibility criteria and search strategy created *a priori* based on *The Cochrane Handbook of Systematic Reviews*.⁶ The databases searched included the Cochrane Library, MEDLINE, PubMed, and the Web of Science, and the time period was from the time of database inception to the present. The search question was the following “How are allostatic load biomarkers utilized to predict objective growth patterns in children?” Each individual biomarker associated with AL was also queried. For example: “How are C-reactive protein measurements utilized to predict objective, physical health outcomes across pediatric populations?”

The search was conducted by a reviewer who assessed the abstract for inclusion criteria, and then examined each full-text report for quality assessment and data extraction. Inclusion criteria included: English language; all ages, races, ethnicities, and genders; studies that used biomarkers linked with objective health outcome data; randomized controlled trials (RCTs), meta-analysis, longitudinal studies, cross-sectional studies, prospective and retrospective review studies; and those studies published within the past decade (2000–2010). Failure to meet one of these criteria resulted in study exclusion. When in doubt, the complete article was screened using the same criteria. Information extracted during the literature review for each individual AL parameter included AL parameter measured; age of pediatric population studied; and method of measurement or collection of the AL parameter.

Study Results

We reviewed 1,362 abstracts: 569 from MEDLINE and 741 from Web of Science. Of those abstracts, 137 met inclusion criteria and were reviewed. From the articles reviewed, an additional 19 articles were added from article references. We examined each of the major

AL coordinated systems, specifying the disease stage captured (primary, secondary, or tertiary), indicating the percent of studies that included children, and the association of each categorical biomarker with growth (Table 2, see page 254).

Sympathetic Nervous System—In the current medical literature, there are few pediatric studies that examine the direct correlation between urinary or plasma catecholamines and growth pattern measurements, and within those few studies there are conflicting data. One study found no association between BMI z-score and urinary catecholamine excretion, but examined a population of children with obstructive sleep apnea.⁷ The other study did find a relationship between the growth measurements fat mass and BMI with 24-hour excretion rates of catecholamines.⁸ Both studies looked at a population ranging from 5 to 19 years of age. The studies that were excluded from this review examined the association of urinary and plasma catecholamine levels with other outcomes or mediators, including hypertension, exercise, caffeine administration, and sleep apnea, and not with growth pattern measurements. No recent studies have investigated plasma catecholamine levels or looked at the pre-school (below age 5 years) population.

HPA Axis—In the adult population, high cortisol levels are associated with obesity, especially abdominal obesity, but in the pediatric population the data are conflicting. Current literature exploring the correlation between cortisol and growth measurement in children looks at salivary cortisol, serum cortisol, urinary cortisol, and dexamethasone suppression testing. Our review found that even within each methodology of cortisol collection there is variability in conclusions.^{9,10} Barat and colleagues¹¹ examined both plasma cortisol and salivary cortisol within the same population of prepubertal (6 to 12 years) children and found that truncal distribution of fat mass, measured by a dual-energy X-ray absorptiometry (DEXA) scan, correlated positively with morning plasma cortisol but correlated negatively with rise of salivary cortisol. The range and variability of conclusions within the pediatric population shows the need for further research as well as the need for consistent collection methods across studies.

Dehydroepiandrosterone sulfate (DHEAS) is an endogenous natural steroid hormone and one of the most abundant circulating androgens in men and women. The majority of current medical literature in pediatric populations shows that peripubertal obesity is associated with hyperandrogenemia, with elevated DHEAS. All the studies in this review showed a direct correlation between BMI or weight and DHEAS level in older children. However, one study that used waist-to-hip ratio (WHR) as a marker of abdominal obesity showed a negative correlation between WHR and DHEAS level.¹²

Metabolism and Lipid Profiles—The fasting lipid panel, or at least one or more lipid components, was collected in almost 25% of all pediatric studies that correlated to growth predictor measurements. The most commonly analyzed lipid was triglycerides, with 26% of studies examining this parameter. The majority of triglyceride studies revealed high plasma triglycerides associated with all measures of adiposity, including BMI, sum of four skinfold thicknesses, waist circumference, and waist-to-height ratio.

In Freedman and colleagues' ¹³ cohort study, the only adult lipid marker with a positive correlation to childhood BMI (subjects age 2 to 17 years) was triglycerides measured 17 years after the first collection point, which shows its potential importance in predicting growth. Another cohort study reported an inverse correlation between childhood BMI at age 9 years and triglycerides and total cholesterol at age 50 years. ¹⁴ However, some studies showed no significant association between BMI or fat mass and triglyceride levels. ¹⁵ Despite these few conflicting studies, triglyceride levels have a strong association with growth prediction in 38 studies reviewed.

Total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were reported in 15% to 20% of the studies, with relatively consistent findings. Elevated TC, elevated LDL, and decreased HDL were associated with increased BMI, waist circumference, skinfold thickness, and fat mass. Very few studies showed conflicting data. In another compelling study, BMI increased more in hypercholesterolemic girls (high LDL) compared to non-hypercholesterolemic girls 5 to 6 years of age over a 6-year period. ¹⁶

The homeostatic model assessment of insulin resistance (HOMA-IR) is a method to quantify insulin resistance and beta cell function; it is calculated using a fasting insulin and glucose serum level. This parameter was calculated in 13% of the pediatric studies and was one of the more common parameters associated with growth pattern predictors. All of the studies that measured HOMA-IR found a positive correlation with increased BMI, whole body fat mass, truncal distribution of fat mass (calculated by [subscapular + waist]/[hip+ thigh] fat mass), waist circumference, weight, subscapular skin-fold thickness, and visceral adiposity. ¹⁵

Of the glucose and insulin markers, HbA1c was the least studied in the pediatric studies, with only 2% of the studies collecting this data. Although one study showed no statistically significant correlation with HbA1c and body composition reported by DEXA scan, other studies found a significant correlation with higher BMI (> 99th percentile) associated with elevated HbA1c levels. ¹⁷ None of the studies that collected HbA1c did so in the preschool population but instead focused on children ages 6 to 17 years.

Fasting insulin was reported in approximately 19% of all pediatric studies. With few exceptions, most studies reported a positive correlation with increasing fasting plasma insulin as a predictor of overweight or obese growth patterns. ¹⁸ These growth prediction measurements included truncal distribution of fat, waist circumference, intra-abdominal fat area, skinfold thickness, body fat percentage, waist-to-height ratio, and ponderal index, with the most commonly used measurement being BMI z-score or BMI. Butte and colleagues ¹⁹ found that fasting insulin, along with leptin, ghrelin, and total T3, were independent predictors of child weight gain over 1 year in children ages 4 to 19 years, whereas Freedman and colleagues ¹³ showed that childhood BMI (children ages 2 to 17 years) did not correlate with adult insulin levels collected 17 years later. Preschoolers (2 to 6 years) demonstrated an association with elevated insulin levels and BMI, and ponderal index was associated with elevated insulin levels. ¹⁶

In these studies, gender differences in growth patterns reflected in the different biomarker associations were noted. For example, for girls, BMI was significantly related to systolic and diastolic blood pressure, HDL, and triglyceride concentrations. All of these increased with age. For boys, BMI was associated with insulin concentration and only systolic blood pressure.

Immune/Inflammation—C-reactive protein (CRP) was the most commonly measured inflammatory marker in approximately 20% of pediatric studies in this literature review. Consistently, studies showed a positive correlation between elevated CRP and overweight/obesity. Most of these studies were looking at populations greater than age 5 years, but one study collected CRP in 2- and 3-year-old Hispanic children and was the one study that found no association between BMI and CRP levels.²⁰

Other inflammatory markers, including serum albumin, fibrinogen, interleukin-6 (IL-6), and tumor necrosis factor-alpha, were evaluated less frequently but are important to note. Of these markers, serum albumin has the least evidence supported by the literature of a correlation with growth pattern measurements.²¹ IL-6 levels were studied more often and showed variability of correlations. The majority of the IL-6 studies showed a positive correlation between IL-6 levels and BMI and fat mass. Within those, there is variability in results by gender (for example, IL-6 is elevated in obese women but not obese men).²² Fibrinogen, although less frequently studied, consistently had a positive correlation with higher percent fat mass, upper body subcutaneous fatness, and BMI.²³ Tumor necrosis factor-alpha studies, on the other hand, showed variable results.²²

Cardiovascular Values—Heart rate variability (HRV) is determined by 24-hour electrocardiogram/ambulatory blood pressure monitoring and measures overall sympathovagal balance. Decreased HRV, which represents autonomic dysfunction, was seen consistently in obese children defined by BMI.²⁴ There were no studies in children below the age of 11 years, with most studies evaluating children ages 11 to 13 years. Homocysteine correlated significantly with BMI, fat mass, and percent fat mass in some studies.²⁵

Diastolic blood pressure and systolic blood pressure were each measured in approximately 25% of all pediatric studies in this review, making these markers two of the most commonly studied AL markers. In the vast majority of studies, both systolic and diastolic blood pressure significantly correlated with BMI.²⁶ Despite the studies that showed positive correlation, the Bogalusa Heart Study, which initially followed participants ages 2 to 17 years and then again after 17 years, found that childhood BMI did not correlate with adult systolic and diastolic blood pressure.¹³

Adiposity Ratios—Twenty percent of studies evaluated leptin levels and 21% evaluated adiponectin. The majority of the leptin studies showed a positive association between leptin and higher BMI, weight, waist circumference, WHR, fat mass, and fat mass percentage.²⁷ Leptin was found to be an independent predictor of weight gain after a 1-year follow up in Hispanic children ages 4 to 14 years.¹⁹ Fleish and colleagues²⁸ also found leptin to be a positive predictor of increased BMI and total body fat mass in 6- to 12-year old children followed up on average 4.4 years later. Only two of 32 studies found that leptin poorly

predicted relative body weight in a 5- and 6-year follow-up.²⁹ Although adiponectin has been included in most recent AL scores for adults, they have not yet been used consistently in children. The majority of adiponectin studies demonstrated a consistent negative association between adiponectin and growth measures, including BMI, waist circumference, percent body fat, and visceral adiposity, including in young children.³⁰

DISCUSSION

As we strive to understand the pathophysiology of growth patterns that affect child health outcomes and health into adulthood, we look toward what we already know to direct us in what we need to know. The concept of allostasis, maintaining a functional complex regulation and relationship between multiple systems, could provide biomarkers to assess health and the inception of dysfunctional regulation. For adults, the concept is known as AL and can be measured by an AL index. These biomarkers often measure the secondary effects at the organ systems level or the tertiary effects when the disease state is fully manifested. However, as evident from this review, many of the common biomarkers utilized in adults related to overweight/obesity have an inconsistent relationship with a child's growth patterns.

Timing is everything. What is evident in an adult is often inconclusive in a child. For example, from our review of the literature, the measurement of cortisol had clear associations with the degree of abdominal obesity in adults but had conflicting findings in children. This might indicate some type of tipping point in children, when they shift from functional to dysfunctional regulation. It is clear with metabolic biomarkers that whenever the relationship develops, it is likely to be nonlinear in nature. For example, the associations with leptin and ghrelin change from childhood to adulthood, imposing more of an effect in childhood with a weaker relationship noted in adulthood. These relationships are made even more complex, varying with both gender and ethnicity.

It is clear clinicians are adept at diagnosing disease states such as diabetes or hypertension. How can we intervene or even prevent the development of these disease states so commonly associated with overweight/obesity in childhood? Ideally, if we want to change the trajectory of developing these common conditions, we need to consider examining early changes at the cellular level, using something such as an allostatic load index that measures primary mediators. From this systematic literature review, we have identified primary mediator biomarkers that demonstrated a consistent association with pediatric overweight/obesity and represent the major systems involved in allostasis. Therefore, we recommend collecting adiponectin and leptin (markers of adipose tissue); CRP (a marker of inflammation); HOMA-IR, total cholesterol, triglycerides, LDL, and HDL (markers of metabolism), and both systolic blood pressure and diastolic blood pressure (markers of the cardiovascular system).

Future work needs to consider how to collect meaningful, consistent data representing the SNS. Once we begin to apply a more consistent approach to collecting primary mediators such as these, reflective of multiple systems, we can learn when the systems tip towards dysfunctional regulation and disease. As clinicians, this would allow us to first prevent and

then to intervene early. These are the tools of pediatricians to improve child health outcomes, and used wisely they could tip the balance toward childhood obesity prevention.

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TABLE 1**10-Parameter Allostatic Load Index⁴**

System	Biomarkers
SNS activity	12-h urinary epinephrine (µg/g creatine) 12-h urinary norepinephrine (µg/g creatine)
HPA axis	12-h urinary cortisol (µg/g) Serum DHEAs (µg/dL)
Metabolism	Waist-to-hip ratio Total cholesterol Serum HDL cholesterol (mg/dL) Glycosylated hemoglobin (%) (HbA1c)
Cardiovascular	Diastolic blood pressure (mm Hg) Systolic blood pressure (mm Hg)

DHEA = dehydroepiandrosterone sulfate; HDL = high-density lipoprotein; HPA = hypothalamic-pituitary-adrenal; SNS = sympathetic nervous system.

Source: Seeman et al.

TABLE 2

Frequency of Pediatric Studies Measuring Allostatic Load Markers

Systems	Allostatic Load Marker	Disease Stage Captured	% of pediatric studies (n = 156)	Association with Growth Prediction Measurement
SNS Activity				
	12-h urinary epinephrine	Primary	0.6%	No association found between BMI z-score and catecholamine excretion rates
	12-h urinary norepinephrine	Primary	0.6%	No association found between BMI z-score and catecholamine excretion rates
	12-h urinary dopamine	Primary	0.6%	No association found between BMI z-score and catecholamine excretion rates
	24-h urinary epinephrine	Primary	0.6%	Lower epinephrine excretion in overweight children (BMI > 95% and Fat Mass > 85%)
	24-h urinary norepinephrine	Primary	0.6%	Higher norepinephrine excretion in overweight children (BMI > 95% and Fat Mass > 85%)
	24-h urinary dopamine	Primary	0.6%	Higher dopamine excretion in overweight children (BMI > 95% and Fat Mass > 85%)
	Plasma norepinephrine	Primary	0%	n/a
	Plasma epinephrine	Primary	0%	n/a
HPA axis				
	Serum DHEAS	Primary	5.1%	DHEAS directly correlated with increased BMI SDS and weight; WHR and DHEAs negatively correlated
	Salivary cortisol	Primary	1.9%	BMI and TDFM negatively correlated to salivary cortisol; higher cortisol reactivity in OW girls
	Serum cortisol	Primary	1.9%	Negative correlation for OB (BMI), no correlation for OW (BMI), positive correlation for TDFM
	24-h urinary cortisol	Primary	0.6%	No consistent associations with fat indexes (% body fat, fat mass, BMI) and urinary free cortisol
	12-h urinary cortisol	Primary	0.6%	Urinary cortisol is elevated in obese (BMI) group
Metabolism				
	Fasting triglycerides	Secondary	26.3%	Positive correlation with increasing growth predictor measures: BMI, SSFT, WC, waist-to-height ratio, fat mass
	Fasting serum HDL cholesterol	Secondary	21.8%	Negative correlation with increasing growth predictor measures: BMI, SSFT, WC, waist-to-height ratio, fat mass
	Fasting serum LDL cholesterol	Secondary	18.6%	Positive correlation with increasing growth predictor measures: BMI, SSFT, WC, waist-to-height ratio, fat mass
	Fasting insulin	Primary	18.6%	Positive correlation between elevated insulin and increasing growth measurements (BMI, TDFM, WC, IAFA, SFT, BF%, waist-to-height ratio, PI); 2 studies showed no correlation

Systems	Allostatic Load Marker	Disease Stage Captured	% of pediatric studies (n = 156)	Association with Growth Prediction Measurement
	Total cholesterol	Secondary	14.7%	Positive correlation with increasing growth predictor measures: BMI, SSFT, WC, waist-to-height ratio, fat mass
	HOMA insulin resistance	Secondary	12.8%	Positive correlation between HOMA-IR and BMI z-score, WBFM, SSFT, TDFM, WC, visceral adiposity
	Fasting glucose	Secondary	10.3%	Positive correlation with increasing BMI, SSFT, FM, and FM%
	Urinary creatinine clearance/UACR/eGFR	Secondary	4.5%	Positive correlation between waist circumference and eGFR. BMI had positive/no/negative correlations with UACR. Creatinine clearance positive correlation with BMI
	TC/HDL	Secondary	1.9%	Positive correlation with increasing growth predictor measures: BMI, SSFT, WC, waist-to-height ratio, fat mass
	Glycosylated Hgb	Secondary	1.9%	Positive correlation between BMI > 99 and elevated HbA1c. No association between HbA1c and BMI
	LDL/HDL	Secondary	1.3%	Positive correlation with increasing growth predictor measures: BMI, SSFT, WC, waist-to-height ratio, fat mass
Immune/Inflammatory				
	C-reactive protein	Primary	18.6%	Positive correlation with BMI SDS, WC, FM%, PI
	Interleukin-6 (IL-6)	Primary	7.7%	Positive correlation with BMI and FM, varied by gender and ethnicity. No correlation in 3 studies
	Fibrinogen	Primary	5.1%	Positive correlation to %FM, BMI SDS, and upper body subcutaneous fatness
	Tumor Necrosis Factor-alpha (TNF-alpha)	Primary	3.8%	Range of results (positive and negative correlation to BMI and fat mass), variability depending on ethnicity
	Albumin	Primary	1.3%	No correlation found between serum albumin and growth measures
Cardiovascular				
	Systolic blood pressure	Secondary	25.6%	Positive correlation with visceral fat accumulation, BMI, PI, WC, excess body weight, SSFT, BF%
	Diastolic blood pressure	Secondary	23.7%	Positive correlation with BMI, WHR PI, WC, BF%
	Homocysteine	Primary	3.8%	Positive correlation with BMI, FM, %FM
	Heart Rate Variability	Secondary	2.6%	Decreased HRV in OB (higher BMI) children
	Aldosterone	Primary	0%	n/a
Adipose				
	Adiponectin	Primary	21.2%	Negative correlation with BMI, WC, BF %, visceral adiposity
	Leptin	Primary	20.5%	Positive correlation with BMI, weight, WC, WHR, FM, FM%

BF = body fat; BMI = body mass index; DHEAS = dehydroepiandrosterone sulfate; eGFR = epidermal growth factor receptor; IAFA = intrabdominal fat area; FM = fat mass; NW = normal weight; OB = obese; OW = overweight; PI = ponderal index; SDS = standard deviation score; SSFT = sum of skinfold thickness; TDFM = truncal distribution of fat mass; WBFM = whole body fat mass; WC = waist circumference; WHR = waist-to-hip ratio.

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