PEDIATRIC AND MATERNAL-FETAL DIVISION NEWS
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From the Mind of the Chair

Greetings PMF Colleagues and Happy New Year!

As this new year unfolds and we find ourselves amid winter's embrace, I believe it is a perfect time to reflect on the many wonderful experiences of being a member of the ADLM Pediatric and Maternal Fetal Medicine (PMF) Division. I hope others within and outside of our division will see this message as a sign of encouragement to volunteer for one of the many initiatives going on.

From my early days as the PMF Fellow in 2016, I was welcomed into the division with open arms. At that time, I could hardly imagine that I would be writing to you as our division's chair position this year—a year marked by organizational and division restructuring. Fortunately, over the years, our division's leadership has been represented by future ADLM Presidents and Board Members, as well as other emerging leaders within our field, all of whom have prepared us for the changes ahead. In fact, did you know that five out of the last eight ADLM Past Presidents were directly involved with pediatric laboratory medicine?

Now as we continue to move into 2025, I am reminded of the incredible efforts our division has achieved over the years. Specifically, our division has developed policy documents, manuscripts, and scientific symposiums, and has continued to advocate in Washington DC about the urgent need for pediatric reference interval funding and the critical role of laboratory-developed tests (LDTs) in patient care. It is truly inspiring to see all these activities continue to reinforce the ADLM mission—*better health for all through laboratory medicine*.

In this new year, let us take pride in our accomplishments and renew our commitment to pushing boundaries in the division. Together, we will embrace the many opportunities ahead that will allow us to continue making a difference in the lives of our patients. Here's to a year filled with growth, innovation, and shared success. Happy New Year to all!

Please enjoy this newsletter that features two main articles "The ABC's of Pediatric Laboratory Medicine, O is for Obesity" and "Reevaluating Pediatric Cardiovascular Risk: Insights from the i3C Consortium and a Novel Risk Assessment Tool." If you have any questions, ideas or comments regarding the PMF division, feel free to contact me.

Sincerely,

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Table of Contents

The ABC's of Pediatric Laboratory Medicine:
O is for Obesity

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Multiple Wings of Childhood Obesity: Mechanistic Link to Diabetes, Hypertension, and Cardiorenal Syndrome

Prevalence of obesity

Obesity, a clinical presentation of excessive amounts of fat deposited in the body, is a major metabolic threat and a rapidly growing public health issue globally. Obesity in children and adolescents is determined based on their body mass index (BMI), which varies with age and sex. It is defined as having a BMI above the 95th percentile for their specific age and sex group. Centers for Disease Control and Prevention (CDC) categorizes body weight status in children and teens (2-19 years) into 5 classes from underweight, healthy weight, to overweight when the BMI ranges from 85th to 95th percentile, obesity when the BMI is 95th percentile or greater, and severe obesity when the BMI range is 120% of the 95th percentile or greater, or 35 kg/m^2 or greater. The American Academy of Pediatrics (AAP) further expands the category of severe obesity into class 2 obesity when the BMI range is 120% to less than 140% of the 95th percentile or BMI is between 35-40 kg/m^2, and class 3 obesity when BMI range is 140% of the 95th percentile, or BMI 40 kg/m^2.

Worldwide, 2.5 billion (43%) adults (aged 18 years) are overweight. Among them, 890 million (16%) have obesity according to the World Health Organization (WHO) 2024 report. More than 390 million children and young adults between 5 and 19 years old are overweight or obese. 37 million children under 5 years old are overweight or obese (1).

In the US, CDC reported that the prevalence of obesity and severe obesity in the adult population was 40.3% and 9.4%, respectively between 2021 and 2023. The prevalence of childhood obesity has more than tripled from 5.2% in 1971 to 17.2% in 2014. As of March 2020, the prevalence of childhood and adolescent obesity in the US was 19.7%, which costs an estimated $1.3 billion annual spending (2). Complications of childhood obesity include cardiovascular, renal, neurological, endocrine, gastrointestinal, musculoskeletal, pulmonary, as well as psychosocial disorders.

Metabolic consequences of childhood obesity and related diagnostic testing

Dyslipidemia

Obesity-induced dyslipidemia, characterized by elevated low-density lipoprotein-cholesterol (LDL-C) and triglycerides and reduced high-density lipoprotein-cholesterol (HDL-C), is associated with increased free fatty acid concentration in adipocytes and oxidative stress that converts LDL-C into oxidized LDL-C (3). Obesity increases systemic oxidative stress by activating various biochemical mechanisms including superoxide generation from nicotinamide adenine dinucleotide phosphate oxidases, oxidative phosphorylation, glyceraldehyde auto-oxidation, protein kinase C activation, polyol and hexosamine pathways (4).

AAP recommends lipid screening for children and young adults with overweight and obesity as a part of risk factor evaluation for cardiovascular disease (CVD) and chronic kidney disease (CKD). Early morning blood samples after at least 12 hours of fasting are preferred. Dyslipidemia in children is defined as: total cholesterol 200mg/dl, LDL-C 130mg/dl, VLDL-C 31mg/dl, non-HDL-C 145 mg/dl, and TG 100mg/dl for <9 years old or TG 130 for 10-21 years old (3). In children, the target treatment goals are LDL-C <100mg/dl, HDL-C >35mg/dl,

and triglyceride < 150mg/dl. When LDL-C is between 130-159 mg/dl, glucose and dietary control as well as exercise counseling are recommended for 6 months, and statin medication needs to be considered when LDL-C remains >130 mg/dl.

Diabetes mellitus

Type 1 diabetes mellitus (T1DM) is predominantly developed during the pre-pubertal span and is thought to be independent of obesity, resulting from the destruction of pancreatic beta islet cells and thus reduction or absence of insulin synthesis (5). In contrast, the development of type 2 diabetes mellitus (T2DM), a condition of insulin resistance in the peripheral tissues, is tightly associated with obesity. Obesity induces insulin resistance by suppressing insulin receptors in the abdominal and peripheral tissues, which inhibit the entry of glucose into the cell. The increased deposition of visceral and ectopic fat in the abdomen and other organs: kidneys, heart, and liver are associated with an increased production of pro-inflammatory cytokines and fatty acids that are responsible for the development of insulin resistance in childhood obesity (6).

Patients with pre-pubertal obesity are four times more likely to develop T2DM than children with normal BMI. T2DM in early life can further increase the risk of developing cardiovascular, liver, and renal diseases (5). A healthy diet and physical activity are effective ways to prevent or slow the development of T2DM. Assessment of insulin resistance is the best predictor for the development of impaired glucose tolerance and T2DM in overweight and obese children. Assessment of insulin resistance includes fasting insulin and glucose, oral glucose tolerance test (OGTT), insulin tolerance test, hyper-insulinemic euglycemic clamp, and the frequently sampled intravenous glucose tolerance test (6). Although T2DM is rare in children, its prevalence has been rising due to the increased rate of childhood obesity, referred to youth-onset-T2DM (5). It shares the same set of diagnostic criteria as in adults: (a) Classic symptoms of diabetes such as polydipsia, polyurea, and a random blood glucose level $\geqslant$ 200 mg/dl, or (b) A fasting (at least 8 hours or overnight) blood glucose level 126 mg/dl, or (c) Two-hour blood glucose $\geqslant$ 200 mg/dl at an OGTT, when 75 g or 1.75 g/kg of body weight to a maximum of 75 g of anhydrous glucose dissolved in water is administered to the patients, or (d) Glycated hemoglobin (HbA1c) level $\geqslant$ 6.5%, using a method that is certified by the National Glycohemoglobin Standardized Program and standardized to the Diabetes Control and Complications Trial (5).

Hypertension

The American Sixth Joint National Committee Guidelines on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defines hypertension when systolic blood pressure is $\geqslant$ 140 mmHg and/or diastolic blood pressure $\geqslant$90 mmHg (7). There are several mechanistic pathways leading to the development of hypertension during obesity, which include adipocyte dysfunction, neurohormonal activation of the sympathetic nervous system (SNS), activation of the renin-angiotensin-aldosterone system (RAAS), and increased oxidative stress. Obesity leads to increased secretion of adipokines, pro-inflammatory cytokines, leptin, resistin, etc., from enlarged adipocytes, which induce systemic inflammation, SNS activity, and RAAS activity leading to vasoconstriction and sodium retention. Obesity is also associated with the increased circulating concentration of all the components of RAAS including renin, angiotensinogen, and angiotensin II (8). Another major culprit of obesity-related hypertension is oxidative stress is which induces SNS activation, RAAS activation, endothelial dysfunction, vascular dysfunction and impaired pressure natriuresis (4).

Cardiovascular kidney metabolic syndrome (CKMS)

CKMS is a relatively new term proposed by the American Heart Association (AHA), defined as a health disorder attributable to connections among obesity, CKD, and CVD, including heart failure, atrial fibrillation, coronary heart disease, stroke, and peripheral artery disease. A

construct of 4 CKMS stages reflects the pathophysiology, spectrum of risk, and opportunities for prevention and care optimization. Obese populations are more prone to develop CKD and CVD compared to the general non-obese population, moreover, obesity may, directly and indirectly, affect outcomes in CKMS by increasing systemic and local inflammation, insulin resistance, T2DM, systemic blood pressure, and glomerular filtration pressure, among other mechanisms (9). To diagnose CKMS, the selection of testing largely depends on the subtypes of CKMS and should be correlated with the clinical history and presentation in obese and overweight children. Glomerular filtration rate (GFR) and renal panel including blood urea, creatinine, and electrolytes are used to evaluate renal function. Urinary albumin-creatinine ratio, neutrophil gelatinase-associated lipocalin, and kidney injury markers are early and sensitive markers for renal injury. Urine analysis provides a wide range of information on renal damage. Cardiac troponin is taken as a sensitive marker for myocardial damage. B-type natriuretic peptide (BNP) or N-terminal pro-BNP is used for cardiac dysfunction/damage. Diagnosis of diabetes, insulin resistance, and dyslipidemia are helpful in the differential diagnosis and intervention of CKMS subtypes.

Metabolic dysfunction-associated steatotic liver disease (MASLD)

MASLD, previously known as Non-Alcoholic Fatty Liver Disease, refers to the accumulation of excess fat in the liver without the presence of significant alcohol consumption. MASLD is highly prevalent in obese children and can persist into adulthood. It contributes to the development of T2DM, CVD, and CKD and increases the risk of cirrhosis and hepatocellular carcinoma (10).

MASLD can be diagnosed through clinical evaluation, laboratory testing, and imaging studies. Liver function should be assessed by testing direct and total bilirubin, total protein, albumin, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase. Lipid profile and glucose tolerance tests are also useful in diagnosing and monitoring MASLD in obese children.

Summary

The prevalence of childhood obesity has increased at an alarming rate worldwide, leading to significant healthcare costs as well as several unwanted clinical conditions including dyslipidemia, diabetes, hypertension CKMS, MASLD, etc. Early screening and diagnosis and taking a suitable intervention against childhood obesity will potentially reduce the complications at an older age.

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Excerpts from the Literature

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Reevaluating Pediatric Cardiovascular Risk: Insights from the i3C Consortium and a Novel Risk Assessment Tool

When evaluating and managing cardiovascular (CV) risks in children, pediatric clinicians typically adhere to recommendations from professional associations such as the American Heart Association, the American Academy of Pediatrics, and the National Institutes of Health. Pediatric guidelines are typically based on the distribution of risk factors in children by age and sex, or on a single threshold for the majority of ages and both sexes, in contrast to adult guidelines, which are based on data demonstrating the relationship between risk factors and disease. Limited long-term research connecting childhood risk variables to adult CV illness and events is available, and these pediatric thresholds have been relatively arbitrary.

In the January 2025 issue of The Journal of Pediatrics, Haley et al. (1) published a prospective observational study involving 38,589 participants from the International Childhood Cardiovascular Cohort Consortium (i3C) (2,3), including 7 cohorts from the US, Finland, and Australia, representing urban, rural, Black, and White populations. The study followed children aged 3 to 19 years, enrolled in the 1970s and 1980s with follow-up to ages 32-65 years. Of the 38,589 participants, 50% were male, and 15% were Black, with a mean birth year of 1969 (±6.3 years). Most childhood visits began in the early 1980s, with an average age of 11.8 (±3.1 years) at the time of the initial visit, and the average age at cardiovascular events was 47.1 (±7.4 years).

The study aimed to establish a clinically actionable score for assessing adult CV event based on five childhood CV risk factors—smoking, body mass index (BMI), systolic blood pressure (SBP), triglycerides (TG), and total cholesterol (TC). The study calculated age- and sex-specific z-scores for each risk factor, which were then averaged to create a combined risk score. The results showed that for each 1-point increase in the combined risk score, the hazard ratio (HR) for CV events increased by 2.75 (95% CI 2.48–3.06). Individuals with a combined risk score 1.5 or more standard deviations above the median began to experience increased CV risk around the age of 40 (4).

The combined risk score provides a straightforward method of assessing childhood CV risk. Averaging the available data can also be used to approximate the composite score in the event that a risk factor is absent. A 9-year-old girl with no history of smoking, a BMI of 16.6 kg/m² (45th percentile), an SBP of 104 mmHg (64th percentile), triglycerides of 75 mg/dL (borderline high), and a TC of 192 mg/dL (borderline high) are among the clinical cases given in the study that demonstrate the practical application of this instrument. For this child, the combined risk score would be 0, falling within the category corresponding to an HR of 2.03, which more than doubles the risk compared to the

lowest category (i.e., z < -0.5). Additional clinical scenarios were presented, showing that the combined risk score offers a more conservative approach while current practice guidelines may not flag an elevated CV risk (5).

It's also worth noting that the findings from a subset of cohorts with LDL-C data available, suggesting that current clinical guidelines for LDL-C with a threshold of 110 mg/dL (5) for hypercholesteremia may understate the long-term risk of CV events because they are higher than the z-score threshold for increased CV risk.

The study's enormous sample size and long-term follow-up across a variety of populations make it an important contribution. However, underrepresentation of Asian and Hispanic people makes the findings not entirely representative of the US population. In contrast to prior research (6) that has created "Clinical CV Health Charts," this study is unique in that it offers a composite risk score that is derived from the direct observation of childhood cohorts and extrapolated to adult CV events. This combined risk score emphasizes how crucial it is to treat juvenile CV risk factors as a first line of defense against early CV disease. The study highlights that when childhood risk variables are still below the current pediatric limits, measures to reduce adult CV risk should start. Clinicians may be more inclined to suggest early lifestyle modifications, more frequent monitoring, or even cardiac assessments for children who are at risk if they use the composite risk score.

In summary, this study reinforces the idea that early intervention is crucial for preventing CV events later in life and suggests that current pediatric thresholds may need to be adjusted to account for the long-term impact of childhood CV risk factors

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