Adipose Tissue as a Target for Precision Medicine Approaches in Childhood Obesity

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Following the trends of the adult obesity epidemic, and worsened by school disruptions during the coronavirus disease 2019 pandemic, childhood obesity prevalence has reached unprecedented levels. The health implications for this generation are especially concerning, as childhood-onset obesity has more severe health consequences than weight gain that begins in adulthood, including increased risk of type 2 diabetes and diabetes-related complications. The complexity of obesity treatment has been challenging, including remarkable heterogeneity in obesity phenotypes and treatment responses among both adults and children. Many in the field have therefore highlighted a need for precision medicine approaches in obesity treatment across age-groups. This includes a need for precision risk stratification to better target treatment intensity, which will require a better understanding of the earliest stages of metabolic syndrome pathophysiology. The health, function, and distribution of adipose tissue have been established as important determinants of metabolic health in both childhood- and adult-onset obesity, making adipose tissue a promising target for understanding phenotypic heterogeneity in obesity. Here, we provide a brief overview of the current limited understanding of adipose tissue biology during childhood development and discuss opportunities for further research into adipose-centric precision medicine approaches in childhood-onset obesity and type 2 diabetes.

ARTICLE HIGHLIGHTS

- Treatment options for childhood obesity are expanding, but precision medicine approaches, including strategies for precision risk assessment, are needed to appropriately target treatment intensity.
- Parameters of adipose tissue dysfunction are better predictors of metabolic syndrome than body size, and therefore adipose tissue represents a prime candidate for research approaches in understanding the pathophysiology of insulin resistance and in identifying biomarkers of future prognosis.
- Expanded developmental research on pediatric adipose tissue in both mice and humans is needed to understand the pathophysiology of childhood-onset obesity and to develop precision treatment approaches.

The fields of pediatric obesity care and youth-onset type 2 diabetes mellitus (T2DM) treatment are remarkably new, presenting novel challenges to pediatricians as treatments developed in adults gradually make their way into pediatric use. As a result of the climb in childhood obesity prevalence (1), pediatricians can currently expect that approximately one in five of their patients will require some form of intervention to address obesity. Rises in childhood obesity rates have been accompanied by rises in obesity-related complications among children, including a doubling in the incidence of youth-onset T2DM from 2003 to 2018 (2). Prompt, effective treatment of obesity during childhood is therefore necessary to achieve diabetes prevention.

A host of new tools are now available for the treatment of childhood obesity, including antiobesity medications, bariatric surgery, and guidelines and resources for intensive lifestyle treatment. The American Academy of Pediatrics (AAP) recently published its first clinical practice guideline for these treatment options, which included emphasis on the role of "individualized and tailored treatment" (3). However, significant limitations remain, including gaps

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in understanding of obesity heterogeneity, access to obesity care, and understanding of how developmental factors impact metabolic syndrome risk and treatment outcomes in children. In this article we will provide a brief overview of the rationale for precision medicine in pediatric obesity, make the argument for adipose tissue as a promising target for precision risk assessment in obesity, and propose research priorities for the field to increase our understanding of early adipose development and its impacts on childhood obesity outcomes.

CALLS FOR PRECISION MEDICINE APPROACHES IN OBESITY TREATMENT

The causes of obesity and its complications are extraordinarily complex and include biological, environmental, psychosocial, and socioeconomic factors. As such, there is a wide range of "obesity phenotypes" among patients. This may include heterogeneity in the metabolic and behavioral factors that contribute to obesity as well as in the development of obesity-related health complications. Variability in developing health complications has posed a particular challenge in terms of accurately diagnosing and treating obesity. Obesity is characterized by excess adiposity compared with lean mass; however, standard screening and diagnosis measures rely heavily on the easily obtained measure of BMI, which does not account for body composition factors such as the degree or distribution of adiposity. The use of BMI has been criticized extensively for overestimating health risk, leading to the recommendation by multiple medical societies that risk assessment for patients with obesity be based on a comprehensive health evaluation rather than BMI alone (4).

Indeed, some individuals with a BMI that qualifies for obesity may be considered "metabolically healthy," at least for an extended period of their lives. The category "metabolically healthy obesity" (MHO) includes individuals who live with little or no disease burden, or who are able to reverse metabolic syndrome disorders after initiating treatment for "metabolically unhealthy obesity" (5,6). Unfortunately, due to a lack of prognostic biomarkers, the family history is often the clinician's only clue to determine which fate is more likely for an individual patient.

While treatment options for obesity care are currently at an all-time high, substantial limitations remain, which warrant a need for continued research and improved clinical strategies in the field. For each of the three obesity treatment modalities (lifestyle therapy, pharmacotherapy, and bariatric surgery) lack of efficacy has been demonstrated for some proportion of the population (7). Very few studies have included investigation of characteristics of "responders" versus "nonresponders." The studies where such comparisons have been performed have identified a myriad of psychosocial and biological predictors of weight loss response that remain under active investigation (8).

Importantly, targeting individual obesity phenotypes with specific therapeutic strategies appears to be of significant clinical benefit. The extreme case is setmelanotide, a melanocortin 4 receptor (MC4R) agonist that targets specific genetic satiety defects (9); however, even among patients without monogenic obesity, tailoring the weight loss intervention according to obesity phenotype improves weight loss outcomes (10). Multiple groups, including the National Institutes of Health, have therefore published calls for increased research into precision medicine approaches in both adult and pediatric obesity treatment, including the study of heterogeneity in the pathogenesis of T2DM (11,12).

THE ROLE OF PRECISION RISK ASSESSMENT IN GUIDING OBESITY TREATMENT INTENSITY

Unfortunately, lack of access to weight loss interventions remains as by far the most significant obstacle to widespread obesity treatment. Multiple barriers to care exist for each of the three obesity treatment modalities (lifestyle, medication, surgery), including lack of patient access to trained providers and insurance coverage (3,13). The recent wave of GLP-1 agonists has further highlighted issues of patient access, with high prices raising concerns regarding their cost-effectiveness (14), and high demand resulting in shortages and interruptions to both obesity and diabetes treatment (15).

As our resources currently stand, it is simply not feasible to offer effective weight loss interventions to the 20% of all children who qualify based on BMI (1). The current state of availability of obesity treatments therefore necessitates some degree of triage, to ensure effective and equitable delivery of limited resources to those who will benefit the most (16). Furthermore, some groups have expressed concern that the current ubiquity of weight loss treatments exposes patients with MHO to unnecessary medical risk and additional weight stigma. These groups have proposed a "Health at Every Size" approach, which emphasizes that not all individuals with obesity require intensive intervention and the associated risks (17).

The clinician's goal is generally to aid the patient in identifying a treatment where the benefits outweigh the risks, but for any given individual, it can be very difficult to determine how much benefit to future health should be expected. Risk stratification is therefore a key element of precision obesity medicine (Fig. 1). Which patients are at high enough risk that they should be prioritized for or encouraged to pursue an intensive intervention? Which patients are at low enough risk, or have achieved sufficient behavioral change, that they can be reassured and focus can be shifted to maintaining a healthy lifestyle? If weight loss interventions can be targeted to the right patients, at the right intensity, for optimal (but also not needlessly aggressive) effect, this would optimize both risk/benefit profiles for patients and cost-effectiveness for payers. Developing these tools for precision risk stratification will require a detailed understanding of the biology underlying metabolic syndrome risk in obesity and of the pathophysiological differences between MHO and metabolically unhealthy obesity.

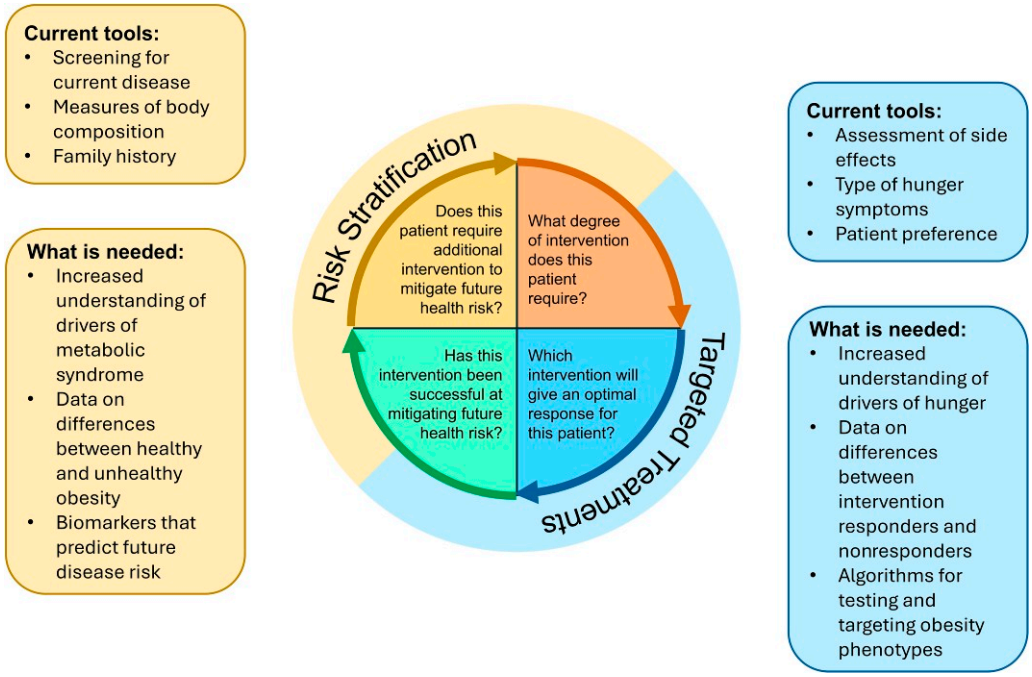

Figure 1—Key questions in obesity precision medicine.

UNIQUE CONSIDERATIONS FOR CHILDHOOD-ONSET OBESITY

Worrisome evidence suggests that the sequelae of childhood-onset obesity may be more severe than those of adult-onset, with increased rates of metabolic syndrome, microvascular diabetes complications, cardiovascular disease, and all-cause premature mortality (18,19). Potential reasons for these differences include increased lifetime exposure to obesogenic stimuli, unique psychosocial challenges of growing up with obesity, decreased use of effective treatment options in the pediatric population, and biological differences in the pathophysiology of obesity during development.

There is therefore a clear role for early intervention during childhood in preventing the development of these more severe obesity-related health consequences. Indeed, resolution of adolescent dyslipidemia prior to adulthood normalizes future cardiovascular risk (20), and bariatric surgery during adolescence improves remission of metabolic syndrome disorders compared with surgery in adulthood (21). In recent ethics discussions regarding fair allocation of GLP-1 agonists, younger patients at highest risk of future health complications were prioritized, with the goal of maximizing benefit to life span (16).

Until recently, options and consensus guidelines for aggressive early intervention in childhood obesity were rather limited. The 2023 AAP clinical practice guideline for the management of childhood obesity, the first of its kind, outlines the treatments available for children with obesity (3). These guidelines include recommendations that intensive lifestyle therapy be offered to all children with obesity, as well as age- and BMI-based criteria for considering pharmacotherapy or bariatric surgery (Table 1).

These guidelines have faced some criticism, largely for the broad range of children to which they apply and the potential risks of increasing childhood exposure to weight stigma or adverse treatment outcomes. To quote a statement published by the Collaborative of Eating Disorders Organizations, which strongly opposed the AAP guidelines, "the medical field tends to overestimate the 'risk' of 'obesity' and maintains that the negative side effects of weight loss treatment outweigh the risk(s) of 'obesity'" (22). The unfortunate truth is that these statements of skepticism and concern do apply for at least some individuals with MHO. There is clearly a population of children and adolescents with obesity for whom early, aggressive intervention is critical to prevent significant disease burden in late adolescence and young adulthood. However, there are also many youth with obesity who will remain metabolically healthy for most of their lives, for whom less intensive treatment approaches would be preferable (23). A key element in the AAP guidelines is that these treatment options are not mandated for every child with obesity; rather, the guidelines emphasize that treatment should be offered and individualized according to the needs of any particular patient (3).

Precision risk assessment strategies are therefore especially needed in the treatment of childhood obesity, where conversations are frequently focused on future risk rather than current disease burden, and the benefits of early intervention must be carefully counterbalanced against the avoidance of unnecessary risks to physical and psychological development. A recent workshop of experts identified several key research gaps in pediatric obesity pharmacotherapy, which included a need for predictive and prognostic biomarkers to guide clinical decision-making (24).

Table 1—Guidelines for obesity treatment options in children

	Age (years)				
	2–5	≥6	≥8	≥12	≥13
BMI criteria	Obesity	Obesity	Obesity	Obesity	Severe obesity
Lifestyle therapy	May offer	Should offer	Should offer	Should offer	Should offer
Pharmacotherapy	—	—	May offer	Should offer	Should offer
Bariatric surgery	—	—	—	—	Should offer

Based on recommendations provided in the 2023 AAP Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents with Obesity. Obesity, BMI ≥95th percentile for age and sex; severe obesity, BMI ≥120% of the 95th percentile. "Lifestyle therapy" refers to "Intensive Health Behavior and Lifestyle Treatment" as defined by the AAP guideline. "Pharmacotherapy" includes both on- and off-label use of several agents listed in the AAP guideline. "Bariatric surgery" refers to both vertical sleeve gastrectomy and Roux-en-Y gastric bypass, discussed in the AAP guideline as the procedures with the best evidence in the pediatric population. —, no recommendation was made for the listed intervention (3).

When children and adolescents present with overt youth-onset T2DM or other metabolic syndrome disorders, their high risk status is clear. However, due to the burden of disease treatment and the more rapid deterioration of youth-onset T2DM, prevention prior to disease onset would be highly preferable, and screening for overt metabolic syndrome during childhood is not sufficient to predict adult risk (23). As in the treatment of adult obesity, the family history is currently the most readily available tool for predicting future risk. However, with higher prevalence of obesity and metabolic syndrome among the current generation of children (1), there is potential for children to develop more severe health consequences than their adult family members as a result of earlier disease onset. Novel precision risk stratification approaches are therefore of paramount importance, to allow pediatricians to target interventions of appropriate intensity, at the appropriate age, to the appropriate patient.

ADIPOSE TISSUE HEALTH AS A DETERMINANT OF METABOLIC RISK

Adipose tissue is a promising target organ for the study of early pathogenic events in the progression of metabolic syndrome and, therefore, for early biomarkers of metabolic syndrome risk. Though often historically maligned as undesirable or dismissed as inert, adipose tissue plays a critical role in health, via both energy storage and endocrine functions. This is illustrated by the example of patients with lipodystrophy, or lack of functional adipose tissue for safe lipid storage, who suffer from the sequelae of systemic lipotoxicity, including severe insulin resistance and hepatic steatosis (25). The last few decades of research have brought the field to the consensus that metabolic syndrome is not a direct consequence of excessive adipose tissue mass but, rather, is a consequence of overloading safe adipose tissue storage capacity, resulting in adipose tissue dysfunction.

Indeed, several forms of heterogeneity in adipose tissue function have been identified as important modifiers of metabolic syndrome risk (Fig. 2). Anatomic distribution is one important variable: expansion of visceral adipose tissue (VAT) has long been associated with insulin resistance independent of BMI, whereas expansion of subcutaneous adipose tissue is protective for metabolic health (26). Sexual dimorphism in adipose tissue distribution, with males tending toward VAT and females toward SAT, contributes to cardiometabolic risks among males (27). Thermogenic adipocytes are another source of variation: specialized for heat generation via rapid lipolysis and oxidation of lipid stores, these can be detected in humans in both discrete brown adipose tissue (BAT) depots and as "beige" adipocytes within white adipose tissue (WAT) depots. Increased thermogenic adipocyte activity inversely correlates with obesity and its complications in humans (28).

The mechanism by which adipose tissue expands in obesity appears to be important for health as well. Adipocyte hyperplasia, or differentiation of new adipocytes from mesenchymal precursors, appears to be metabolically protective, allowing for effective lipid storage with angiogenesis to maintain blood supply and avoid lipotoxicity. The alternative mechanism of expansion is adipocyte hypertrophy, or overfilling of preexisting adipocytes, which is associated with mechanical stress, hypoxia, inflammation, altered extracellular matrix (ECM) remodeling, and fibrosis. Notably, measures of adipocyte hypertrophy, inflammation, and fibrosis are better predictors of metabolic syndrome in adults than BMI, supporting a role for adipose tissue dysfunction in metabolic syndrome pathophysiology that is not dependent on adipose tissue mass (6).

Correlating with the degree of ECM remodeling in WAT, endotrophin, a circulating cleavage product of type VI collagen derived from fibrotic adipose tissue and other organs with fibroinflammatory lesions, is emerging as a powerful biomarker in T2DM and other obesity-related disorders (29). Conversely, adiponectin has emerged as a protective biomarker of healthy adipose tissue, with higher levels in lean individuals as well as individuals with MHO (30). These are just two particularly promising examples of an expanding list of biomarkers secreted by adipose tissue, including traditional adipokines as well as more newly studied adipose-derived exosomes and circulating noncoding RNAs (31,32).

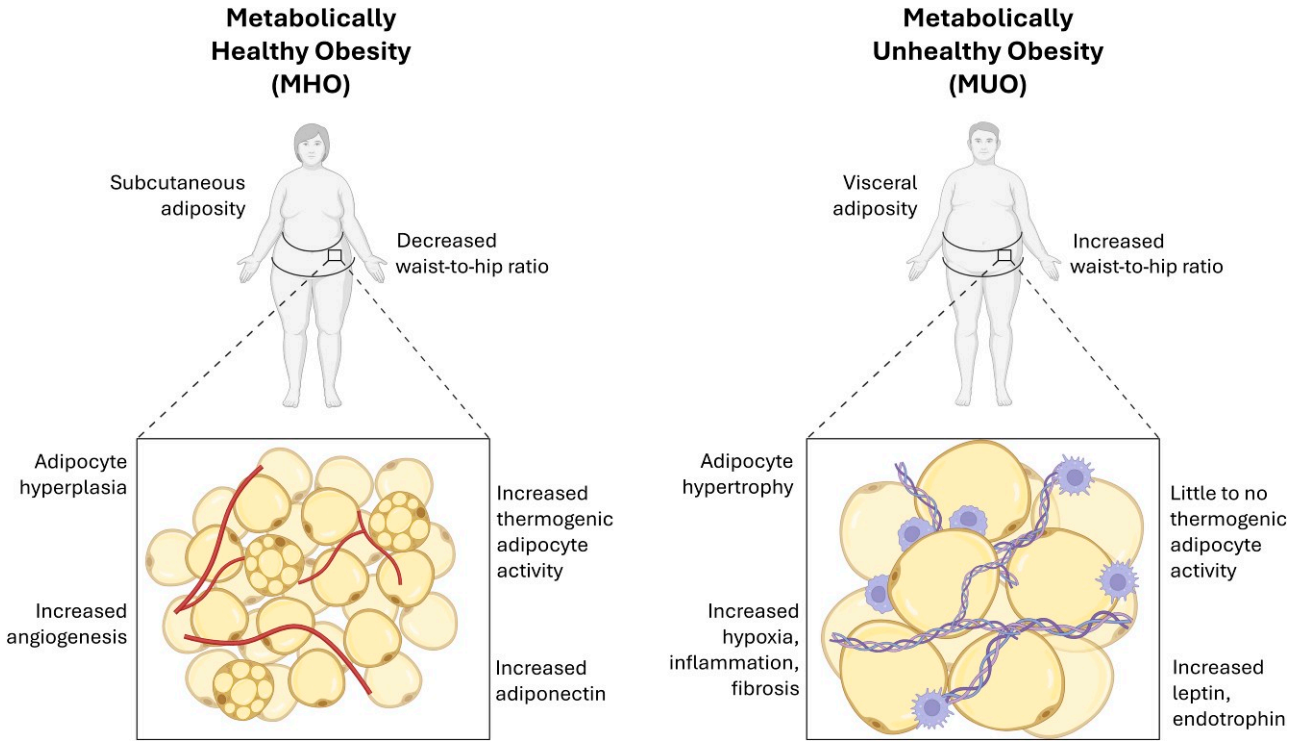

Figure 2—Adipo-centric determinants of health in obesity.

Advanced "-omics" studies in adult obesity have recently made possible the detection of new levels of heterogeneity in obesity biology, many of which continue to point toward adipose tissue as a central player. Genome-wide association studies of T2DM have identified genes involved in adipogenesis and protective adipokines such as adiponectin (33). More recently, single-cell transcriptomic studies on adult human adipose tissue have identified specific subtypes of adipocytes and their progenitor cells, some of which correlate with weight or disease status (34,35). Much work remains to determine the differing functions of heterogeneous adipocytes and preadipocytes in adipose tissue and the mechanisms by which they influence whole-body metabolism.

ADIPOSE TISSUE DEVELOPMENT DURING CHILDHOOD

As far as the field has progressed in terms of understanding adipose biology and pathophysiology in adult obesity, less is known about the development of adipose tissue during childhood, although a few foundational studies have established some basics (Fig. 3). Both WAT and BAT first appear during fetal development, without apparent sex differences, at 14–24 weeks' gestation. Anatomically distinct adipose depots (including both subcutaneous and visceral WAT) are fully established by the 28th week with progressive rises in leptin and adiponectin throughout late gestation (36–38). BAT is highly prominent and critical for temperature regulation at birth but gradually regresses beginning at ∼8 weeks postnatally (39). Several hormonal regulators of fetal growth (e.g., growth hormone, IGF-1, IGF-2, prolactin) are proadipogenic for white and/or brown adipocytes in vitro and are therefore likely to play a role in adipose tissue depot establishment and growth during this time (40).

From birth to 6 months, a time characterized by high nutritional intake with low mobility, white adipose stores expand greatly, most prominently via adipocyte hypertrophy, with a peak in adiponectin levels. From 6 months to 2 years, gross motor skills are gained, energy expenditure increases, and adipocytes gradually decrease in size as their energy stores are released and used. During this time, the positive correlation between adiponectin and adiposity disappears, with the eventual establishment of an inverse correlation between adiponectin and adiposity for the remainder of the life span (41,42).

After early childhood, BMI reaches a nadir prior to an "adiposity rebound," characterized on the cellular level by gradual adipocyte hyperplasia with no significant change in adipocyte size until an acceleration of both hyperplasia and hypertrophy during puberty (41). Establishment of sexually dimorphic adipose patterning begins during early puberty, with the greatest magnitude of sex differences occurring in late puberty and early adulthood (43). The pubertal period is also associated with a transient increase in BAT activity, correlating with the accumulation of muscle mass (44). After adulthood is reached, adipocyte number is largely static, although some degree of hyperplasia occurs as part of adipocyte turnover. Adipocyte number is therefore believed to reach a "set point" in adolescence (45), a

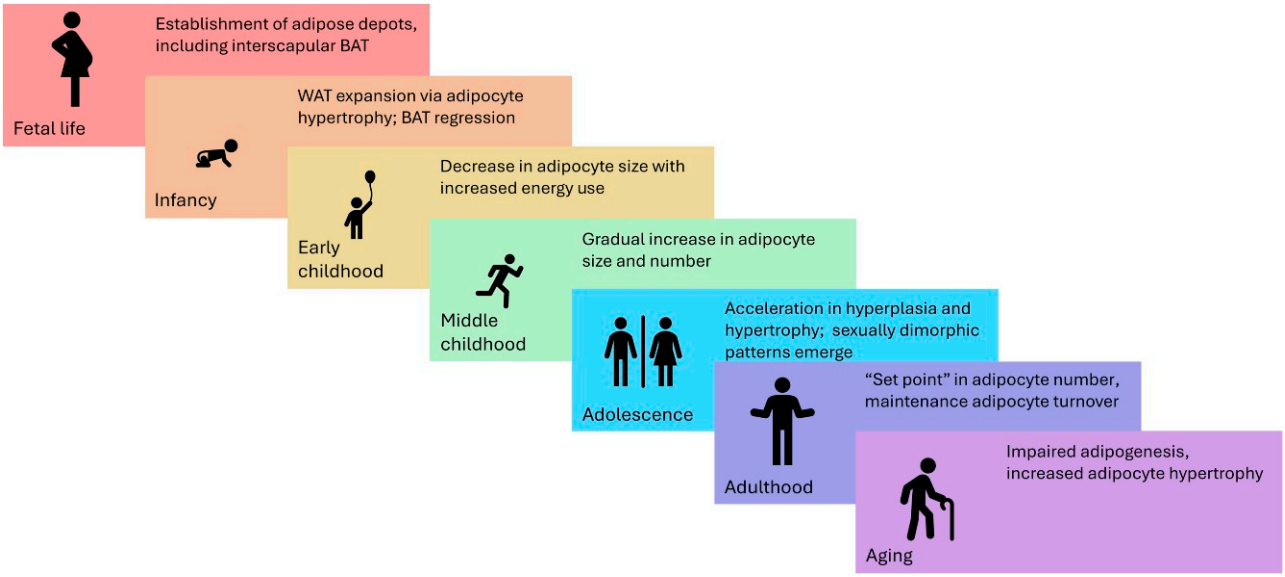

Figure 3—Stages of adipose tissue development in humans.

finding that suggests a strong difference in the plasticity of pediatric versus adult adipose tissue.

THE UNIQUE BIOLOGY OF OBESITY IN DEVELOPING ADIPOSE TISSUE

Many descriptions of basic relationships connecting adipose function to metabolic health in adults also hold true in children. These include findings in pediatric populations that insulin resistance correlates with VAT, adipocyte hypertrophy, adipose inflammation, ECM remodeling, low adiponectin, elevated leptin, elevated endotrophin, and decreased thermogenic adipocyte activity (46–50). Notably, most of the studies with direct analysis of WAT biospecimens have been limited to the adolescent population.

Yet evidence does suggest that obesity during active adipose development may have unique effects that complicate the picture in growing children. Increased visceral adiposity correlates with increased weight gain and formula feeding as early as 3 months old (51). In children and adolescents with obesity, the adiposity rebound often occurs earlier in development (52), and both adipocyte size and number are greater than those of their peers, an effect that is seen even in the youngest subjects studied (2 years old) (41). In adults with obesity, a younger age of obesity onset is associated with a dramatic increase in adipocyte number, with apparent peaks of hypercellularity when obesity begins in early childhood (0–4 years) or early adolescence (9–13 years) (53). These data suggest that the biology of adipose tissue in obesity may be fundamentally different at different stages of development.

Work in preclinical models supports the notion that developmental timing is of significance in the study of adipose biology. Lineage tracing experiments in mice suggest that newly differentiated adipocytes during juvenile mouse development have distinct precursor origins in comparison with those recruited in adulthood (54), and single-cell analysis in perinatal mice has suggested that the increased adipogenic capacity of younger adipose is mediated at least in part by developmental changes in both the composition and the function of adipocyte progenitor cells (55). However, significant limitations exist in the robust application of preclinical models to an understanding of human adipose development. One of the largest barriers is the lack of exact correlates for developmental timing; e.g., mouse adipose depot establishment begins much closer to birth and continues through the immediate postnatal period (56).

Similarly to findings in adults, advanced "-omics" work has provided hints at the importance of adipose tissue function underlying disease risk; however, several factors unique to children have been identified. The first genome-wide association study data for youth-onset T2DM identified two novel genes not previously implicated in adults (*PHF2*, *CPEB2*), both of which have been implicated in adipogenesis or adipocyte function (57), and recent extensive multi-omics profiling of children also implicated several genes with high adipose tissue expression as associated with a metabolically unhealthy phenotype (58). Transcriptomic studies of childhood obesity have identified forms of noncoding RNA that impact adipogenesis or that circulate in adipose-derived exosomes (59,60). Importantly, some of the noncoding RNA elements identified show opposing trends in childhood versus adult obesity, suggesting that developmental factors impact these circulating biomarkers (61).

Of particular importance in the field of pediatric obesity has been the study of epigenetics, especially regarding the contribution of the prenatal environment to childhood obesity. Prenatal factors such as maternal obesity, gestational diabetes mellitus, maternal malnutrition, small for

gestational age, and intrauterine growth restriction have long been implicated in the later development of childhood obesity and metabolic syndrome (62). Some studies on intrauterine factors have identified transgenerational impacts on adiposity and health that suggest an epigenetic effect (63). Epigenome-wide association studies of adult adipose tissue have identified several depot-specific methylation variations that correlate with obesity and effects on adipogenesis and adipocyte function, although prenatal exposures were not evaluated (64). Epigenome-wide association studies analyses have not yet been conducted directly on adipose tissue from children; however, those performed on more accessible tissues have shown an association between maternal obesity during pregnancy and methylation changes in offspring, including some persistence into adolescence (65).

Studies on the effects of premature birth have also highlighted the importance of late gestation as a critical time in adipose tissue development. Premature infants have higher adiposity during catch-up growth than term infants, and go on in adulthood to have increased adiposity, including visceral adiposity, and worsening of several measures associated with the metabolic syndrome (66). While the adipose tissue of premature infants has not yet been directly studied, relative deficiencies of IGF-1, adiponectin, and especially leptin during the perinatal period point to a high likelihood of aberrant adipose tissue development (40).

Finally, aging studies in humans have provided further evidence for dynamic changes in adipose biology across the life span. Aging has been associated with impaired adipogenesis, decreased thermogenic adipocyte activity, impaired angiogenesis, and increased adipose tissue inflammation in humans (67). Notably, declines in the differentiation capacity of adipocyte precursors begin as early as 30 years old, and this limited capacity for adipocyte replenishment results in increased proportions of older, hypertrophied adipocytes (68). Certain preclinical models have suggested that accelerated adipogenesis in juvenile mice could result in an "accelerated aging" of adipose tissue with early depletion of precursors (69). Whether childhood-onset obesity might result in accelerated adipose aging or depletion of adipocyte precursors in humans remains unknown.

APPROACHES NEEDED IN THE FIELD OF PEDIATRIC ADIPOSE TISSUE

Despite recent advances in applying innovative research techniques to the problem of childhood obesity, much of the above is based on association studies that cannot delineate causality, and adipose tissue from pediatric patients has been directly studied in very few instances. While the procurement of tissue from pediatric patients is necessarily challenging and requires carefully regulated consent, enrollment, and tissue collection procedures, several groups have done so with success, enabling our current understanding of human adipose development as described above. However, much work remains to be done for the field of pediatric adipose biology to catch up to our understanding of adult adipose and to better understand the unique biology of obesity during active adipose development (Fig. 4).

Understanding the pathophysiology of childhood obesity on a cellular level will require ambitious multi-omics

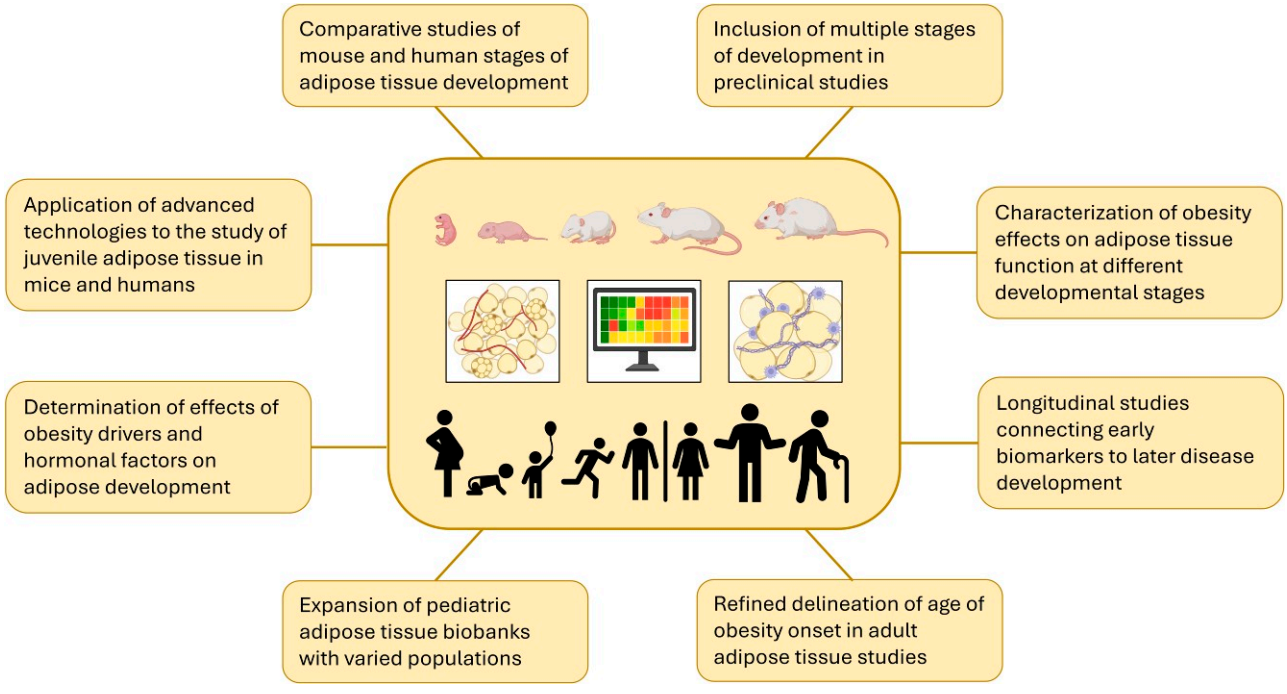

Figure 4—Research priorities for the study of adipose tissue development and the impacts of childhood-onset obesity.

work to delineate the heterogeneous cellular composition and functionality of adipose tissue across all stages of childhood development, from the fetal period through completion of adolescence. Several understudied areas will need to be addressed, including increased study of adipose tissue in infancy and early childhood, thorough characterization of the patterns and mechanisms of sexually dimorphic patterning during puberty (including effects of variations in pubertal timing), study of effects of common exposures that influence obesity outcomes (e.g., prematurity, intrauterine factors, environmental factors), and analysis of effects of weight gain on adipose tissue during key developmental windows. These efforts will necessitate robust biobanking of adipose tissue from children who vary by age, weight status, metabolic status, and other biological factors.

Aside from the direct study of pediatric adipose tissue, investigators in ongoing studies in mice, children, and adults should be mindful of age and developmental stage as biological variables in the pathophysiology of obesity, to determine whether there are critical developmental windows that alter obesity outcomes. Advanced methodologies should be applied to the robust study of adipose tissue in juvenile mice as well, including comparative studies to align as closely as possible the timing of key developmental periods between mouse and human development. Furthermore, preclinical studies investigating adipo-centric treatment effects should be expanded to include juvenile mice so that developmental impacts on treatment response can be assessed. Longitudinal studies spanning multiple developmental stages should be performed wherever possible, and emerging biomarkers should be analyzed not just for correlation with current metabolic state but also for prediction of future disease risk. Finally, adult studies of adipose tissue should include age of obesity onset as a variable, to better delineate the long-term effects of obesity onset at different developmental stages on adipose tissue function.

For now, biomarkers to predict future disease risk remain limited. While the clinical utility of genetic testing has expanded for the diagnosis of appetitive disorders that cause obesity, genetic testing to determine future metabolic syndrome risk remains an understudied area. Pending innovations in precision risk assessment for pediatric obesity, clinicians and patients would benefit from an individualized treatment approach that takes into careful consideration available measures and predictors of weight-related health risk (Fig. 5) as well as patient- and family-centered treatment goals, which may include additional factors such as improvement in physical function.

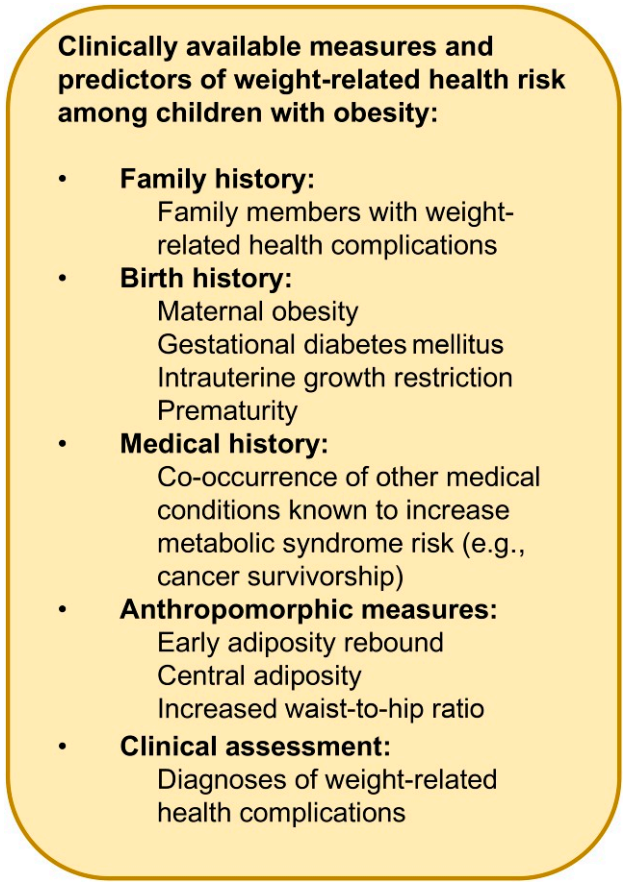

Figure 5—Clinically available measures and predictors of weight-related health risk among children with obesity.

DISCUSSION

While the new era of obesity pharmacotherapy has provided clinicians and patients with expanded treatment options, substantial challenges remain in the field of pediatric obesity medicine. We agree with calls within the field for increased research into precision medicine approaches for childhood obesity. Furthermore, we propose that precision risk assessment should be an area of prime focus, to provide clinicians with tools for risk stratification and triage of limited treatment resources. While ongoing work in the metabolic heterogeneity of pancreatic and hepatic function in the pathogenesis of insulin resistance remains vital, adipose tissue, with its role at the heart of obesity-related pathophysiology, represents an understudied target for researchers seeking biomarkers and predictors of cardiometabolic disease. For understanding and combatting the unique challenges of childhood-onset obesity and youth-onset T2DM, increased research will be needed to delineate the detailed cellular development of adipose tissue from infancy to adolescence, and to identify the earliest steps of metabolic syndrome pathogenesis in children with obesity.

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