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BRIEF CUTTING EDGE REPORT

Pediatric Obesity

Fat content in infant mesenchymal stem cells prospectively associates with childhood adiposity and fasting glucose

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Abstract

Objective: In human studies, new model systems are needed for improved mechanistic investigation of developmental predisposition for metabolic disease but also to serve as benchmarks in early life prevention or intervention efforts. In this regard, human infant umbilical cord–derived mesenchymal stem cells (MSCs) are an emerging tool. However, long-term clinical relevance to *in vivo* markers of metabolic disease is unknown.

Methods: In a cohort of 124 mother/child dyads, this study tested the hypothesis that triglyceride content (TG) of infant MSCs undergoing adipogenesis *in vitro* (MSC-TG) is associated with *in vivo* adiposity (percent fat mass) from birth to early childhood and with fasting glucose and insulin in early childhood.

Results: MSC-TG was positively associated with *in vivo* child adiposity at birth, age 4 to 6 months, and age 4 to 6 years. MSC-TG was associated with fasting glucose, but not insulin, at 4 to 6 years. Importantly, MSC-TG explained an additional 13% variance in child adiposity at 4 to 6 years, after accounting for other established birth predictors (weight and percent fat mass at birth) and other established covariates related to child adiposity (e.g., breastfeeding exposure, physical activity).

Conclusions: This work demonstrates the strength of the MSC model for predicting offspring metabolic phenotype into childhood, even when considering the important contribution of other early life risk factors.

Lauren E. Gyllenhammer and Allison M. Duensing contributed equally to this study.

INTRODUCTION

Adverse early life/fetal exposures such as overnutrition or stress can have profound effects on the health and disease risk of the offspring [1], yet there is a fundamental gap in our understanding of the molecular underpinnings of the developmental origins of obesity and diabetes in humans [2, 3]. Development of new tools and models for understanding these pathways, particularly those that can be measured at birth or shortly thereafter, is critical for identification of children most at risk for childhood obesity and can serve as early benchmarks in prenatal interventions or early life primary prevention efforts.

In our previous work, we employed a human infant umbilical cord–derived mesenchymal stem cell (MSC) model to investigate offspring adipogenesis and metabolism outcomes with intrauterine obesity exposure. *In utero*, fetal MSCs are the progenitors for mesodermal tissues, including adipose and skeletal muscle. We previously demonstrated that MSCs from infants exposed to obesity *in utero* have greater capacity for adipogenic differentiation and higher fat content when cultured and differentiated *in vitro* [4], by mechanisms similar to animal models [5, 6]. Furthermore, fat content of MSCs undergoing adipogenesis positively correlates with neonatal adiposity *in vivo* [4], suggesting clinical relevance of the MSC model. However, this early work was conducted in a small subset of infants from 29 mothers with obesity or normal weight and was limited to neonatal measures of adiposity. Hence, the goal of this study is to substantiate the *in vivo* relevance of the MSC model beyond infancy, within a larger racially diverse cohort.

Study Importance

What is already known?

- Human mesenchymal stem cells (MSCs) are an emerging model to investigate developmental predisposition for altered body composition and metabolic disease.
- The fat content of MSC-derived adipocytes is associated with *in vivo* adiposity in infancy in preliminary studies. The larger clinical relevance is unknown.

What does this study add?

- We show for the first time that the association of MSC fat content with *in vivo* adiposity extends beyond infancy to children 4 to 6 years of age.
- Fat accumulation in MSC-adipocytes is a better predictor of early child adiposity than other established neonatal predictors, and it is associated with fasting glucose at 4 to 6 years.

How might these results change the direction of research or the focus of clinical practice?

- This work substantiates the clinical relevance of MSCs for *in vivo* physiology in children up to 4 to 6 years.
- This work highlights the utility in collecting MSCs at birth in future mechanistic and intervention studies aimed at offspring metabolic health.

METHODS

Population

We collected, cultured, and cryopreserved MSCs from a convenience subsample of 165 infants born to mothers participating in the longitudinal Healthy Start cohort study [7], as described previously [4, 7]. Women were eligible for enrollment in the parent study if they were ≥ 16 years of age with a current singleton pregnancy ≤ 23 weeks of gestation. Exclusion criteria included a history of prior diabetes, premature birth, or serious psychiatric illness. Here, we examined 124 mothers and infants with viable MSC cultures that were successfully differentiated to adipocytes and paired child adiposity data. The Colorado Multiple Institutional Review Board approved the Healthy Start study (ClinicalTrials.gov, NCT02273297), and all participants provided informed consent.

Maternal assessments

Maternal data collection for the Healthy Start study has been previously described [7]. Mothers self-reported their race and ethnicity. We categorized [8] women as non-Hispanic White, non-Hispanic Black, Hispanic, or other because of small numbers in additional categories. Women filled out questionnaires at 6 months post partum to evaluate duration and exclusivity of breastfeeding, categorized as exclusively breastfeeding ≥ 6 months or as not exclusively breastfeeding at 6 months (including those who had never breastfed).

Child metabolic and body composition measures

We obtained infant birth weight from medical records and study staff measured child weight, length, and body composition (fat-free mass percentage [FM%]; whole-body air plethysmography [PEAPOD/BOD-POD, COSMED, Inc.]) at each postnatal visit: neonate $n = 124$ (24–72 hours after birth), infant $n = 122$ (age 4–6 months), and early childhood $n = 70$ (age 4–6 years). Early childhood body mass index (BMI) z score was calculated based on Centers for Disease Control and Prevention growth charts (based on sex and age). We collected a fasted venous blood sample for measures of insulin and glucose ($n = 51$) at the 4- to 6-year visit. We assessed child Healthy Eating Index and physical activity levels (daily steps) using 2-day dietary recalls and 7-day triaxial accelerometry, as described previously [9].

TABLE 1 Maternal and child characteristics (n=124)

	Mean (SD) or n (%)	IQR
Maternal		
Age (y)	28.5 (6.1)	10
Prepregnancy BMI (kg/m^2)	25.0 (5.1)	6.1
BMI categories, n		
Underweight	3 (2%)	-
Normal weight	63 (51%)	-
Overweight	41 (33%)	-
Obesity	17 (13%)	-
Race and ethnicity, n		
Non-Hispanic White	68 (55%)	-
Hispanic	33 (27%)	-
Non-Hispanic Black	14 (11%)	-
Other	9 (7%)	-
Gestational diabetes, n[a]	7 (6%)	
Cesarean delivery, n	21 (17%)	-
Nulliparous, n	67 (54%)	-
Insulin (μIU/mL)	13.7 (11.8)	8
Glucose (mg/dL)	79.4 (8.7)	9
FFA (uEq/L)	404 (143)	169
Triglycerides (mg/dL)	160 (50.5)	72
Child		
Females, n	53 (43%)	-
Infant feeding mode, n[b]		
Ever breastmilk fed	118 (97%)	-
Fed breastmilk at 6 months	84 (67%)	-
Exclusively fed breastmilk at 6 months	52 (43%)	-
Neonate		
Gestational age at birth (wk)	39.5 (1.3)	1.4
Birth weight (g)	3270 (431)	573
SGA, n	10 (8%)	-
BMI (kg/m^2)	12.9 (1.2)	1.4
Fat mass (%)	9.4 (4.2)	5.6
MSC-TG ($\log_{10}$)	−0.1 (0.2)	0.2
4–6 months		
Age (mo)	0.4 (0.1)	0.1
BMI (kg/m^2)	16.7 (1.6)	2.3
Fat mass (%) (n = 112)	24.8 (5.6)	8.9
4–6 years		
Age (y)	4.6 (0.3)	0.1
BMI (kg/m^2)	15.6 (2.2)	1.2
Fat mass (%) (n = 70)	19.4 (7.1)	8.4
Insulin (μIU/mL)	6.6 (5.2)	3
Glucose (mg/dL)	82.2 (6.9)	8

Abbreviations: FFA, free fatty acid; MSC, mesenchymal stem cell; MSC-TG, adipocyte triglyceride (TG) accumulation in MSCs after 21 days of adipogenesis; SGA, small for gestational age.
[a]n = 6 missing gestational diabetes data.
[b]n = 50 missing infant feeding mode data.

MSC culture, differentiation, and measures

Our methods for MSC culture from fresh umbilical cord tissue explants and MSC adipogenesis have been described in detail [4, 10]. We harvested MSCs after 21 days of adipogenesis to measure adipocyte triglyceride (TG) storage (MSC-TG). We extracted total lipids using the method of Bligh and Dyer [11]. We measured TGs using a commercially available kit (Sigma-Millipore) then normalized values to protein content measured via bicinchoninic assay (BCA, Thermofisher).

Statistical methods

Statistical analyses were performed with SAS software version 9.4 (SAS Institute Inc.) with $\alpha = 0.05$. MSC-TG, child FM%, and fasting insulin were $\log_{10}$-transformed to achieve normal distributions. We examined the relationship between MSC-TG and child adiposity (i.e., FM%) separately at birth, 6 months, and 4 to 6 years by regressing child FM% on MSC-TG using linear regression. We adjusted all models for infant sex and child age at body composition measure (including gestational age at birth for infancy models). We additionally included the following sociodemographic and postnatal covariates in statistical analyses depending on child age/model: maternal race and ethnicity, maternal prepregnancy BMI, infant feeding mode, child Healthy Eating Index, and physical activity at 4 to 6 years. We additionally reported the relationship between MSC-TG and child BMI z score at 4 to 6 years, a commonly reported child adiposity proxy.

Next, we examined whether the association between MSC-TG and FM% at 4 to 6 years was independent of weight and/or FM% at birth. Using stepwise models, we quantified the relative R^2 gained from each predictor. Finally, we examined the linear relationship between MSC-TG and fasting metabolic measures (i.e., glucose and insulin) at 4 to 6 years with and without adjustment for covariates.

RESULTS

Maternal and child characteristics are presented in Table 1. The characteristics of this sample did not differ notably from the characteristics of all potentially eligible participants in the Healthy Start cohort [4].

MSC-TG is associated with child adiposity from birth to 4 to 6 years

TG content of MSCs undergoing adipogenic differentiation (MSC-TG) was positively associated with child FM% at birth, 6 months, and 4 to 6 years. These relationships remained significant after controlling for maternal race and ethnicity, prepregnancy BMI, and established postnatal covariates related to child adiposity [12] (at birth: $\beta = 0.20$,

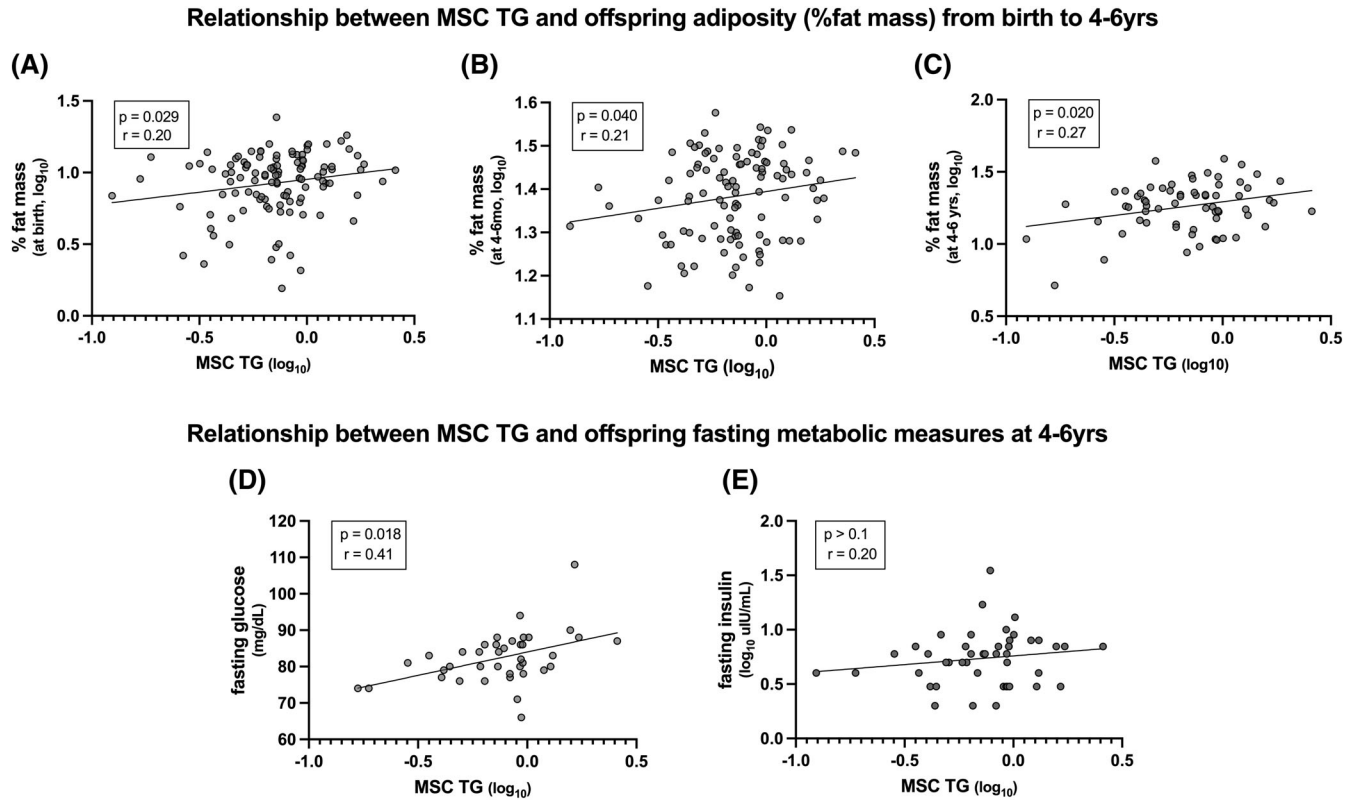

FIGURE 1 Mesenchymal stem cell–triglyceride (MSC-TG) content is associated with child adiposity from birth to 4 to 6 years and child fasting glucose at 4–6 years. MSC-TG content is positively associated with child percent fat mass (FM%) at (A) birth, (B) 4 to 6 months, and (C) 4 to 6 years. MSC-TG content is positively associated with child (D) fasting glucose but not (E) fasting insulin. Analyses were performed by linear regression model with adjusted *p* values presented. For ease of interpretation, partial Pearson correlation coefficients are additionally provided in the figure (each correlation is adjusted for child age at scan, child sex, and gestational age at birth for the infant scans [at birth and 4- to 6-month scans])

TABLE 2 Birth predictors associated with childhood adiposity

	β	Total model R^2	Additional variance explained (R^2m)	*p* value
Model 1 (outcome FM% at 4–6 years)				
Covariates only		0.07		
+ Birth weight	0.00004	0.08	0.01	0.6171
+ FM% at birth	0.26067	0.17	0.10	0.0619
+ MSC-TG content	0.24544	0.23	0.16	0.0224*
Model 2				
Covariates + birth weight + FM% at birth		0.19		
+ MSC-TG content	0.22677	0.32	0.13	0.0412*

Note: Results of linear regression models. Covariates were maternal race and ethnicity, maternal prepregnancy BMI, child age at adiposity measure, child sex, breastfeeding exposure, diet quality, and physical activity levels at 4 to 6 years. Model 1: The R^2 reported for covariates only is given. Each predictor was then added to the model separately. The R^2m reported refers to the R^2 of the predictors(s) over covariates alone. Model 2: The R^2m reported for MSC lipid content refers to the R^2 of this predictor over a model including covariates, birth weight, and FM% at birth.
Abbreviations: FM%, percent fat mass; MSC, mesenchymal stem cell, TG, triglycerides.
*$p < 0.05$.

$p = 0.036$; adjusted $\beta = 0.22$, $p = 0.023$; 4–6 months: $\beta = 0.08$, $p = 0.052$; adjusted $\beta = 0.08$, $p = 0.046$; 4–6 years: $\beta = 0.19$, $p = 0.023$; adjusted $\beta = 0.26$, $p = 0.022$; Figure 1A–C). MSC-TG was not associated with child BMI *z* score (4–6 years: $\beta = 0.87$, $p = 0.20$; adjusted $\beta = 0.72$, $p = 0.28$).

MSC-TG is associated with child fasting glucose at 4 to 6 years

MSC-TG was positively associated with child glucose levels at 4 to 6 years, with and without controlling for sociodemographic and

postnatal covariates ($\beta = 12.0$, $p = 0.013$; adjusted $\beta = 15.0$, $p = 0.020$; Figure 1D). However, MSC-TG was not related to child insulin levels at 4 to 6 years ($\beta = 0.18$, $p = 0.221$; adjusted $\beta = 0.04$, $p = 0.863$; Figure 1E). In post hoc analysis, we tested whether the relationship between MSC-TG and glucose was dependent on child adiposity. When adding FM% at 4 to 6 years to the model, the relationship between MSC-TG and fasting glucose remained significant (adjusted $\beta = 17.9$, $p = 0.029$), indicating the MSC-TG association is independent of child adiposity.

MSC-TG predicts child adiposity

We examined MSC-TG as a predictor of child FM% at 4 to 6 years, relative to other established neonatal predictors (Table 2), accounting for sociodemographic and postnatal covariates that can contribute to childhood adiposity. Importantly, MSC-TG explained 16% of the variance of child FM% at 4 to 6 years, versus 10% explained by FM% at birth and 1% explained by birth weight. Additionally, when all three neonatal predictors were included in the model, MSC-TG was the only significant and independent predictor of child FM% at 4 to 6 years and continued to explain 16% of the variance of child adiposity.

DISCUSSION

MSCs are the progenitors for tissues highly pertinent for childhood obesity and metabolic disease risk: adipose and skeletal muscle. Here, we show during *in vitro* adipogenic induction, MSC fat content (i.e., MSC-TG) reflects the *in vivo* fat content in the child from birth to 4 to 6 years. Although childhood obesity has a multifactorial and complex etiology, our data suggests that a susceptibility and propensity toward fat accumulation is present and measurable in stem cells collected at birth. Furthermore, MSC-TG is positively associated with fasting glucose at 4 to 6 years independent of a child's current adiposity, suggesting an additional relationship between stem cell phenotypes and early markers of metabolic health. We note that this relationship exists in a population of primarily normoglycemic children. Nevertheless, childhood variation in fasting glucose levels, even in the normoglycemic range, can predict adult risk for prediabetes and type 2 diabetes, with values in the 86–99 mg/dL range associated with a > 2-fold increased risk compared with children with < 86 mg/dL [13].

A growing body of work, by ourselves [4, 10, 14, 15] and others [16, 17], indicates that infant MSCs are sensitive to the intrauterine environment. With intrauterine obesity exposures, MSC epigenetic and metabolic phenotypes mirror animal models of gestational obesity and adult humans with established obesity. We show here for the first time that the association between MSC fat content prospectively associates with adiposity and metabolic health into childhood. Our findings are strengthened by the use of repeat precision adiposity measures, FM%, which more closely approximate risk for cardiometabolic diseases, rather than commonly employed body composition proxy measures (e.g., BMI) [18, 19]. Although MSC fat content was significantly associated with the precision adiposity measure, FM%, in early childhood, MSC-TG was not associated with BMI *z* score. Child BMI as a clinical marker has known limitations, particularly its inability as a weight-based measure to discriminate between lean and fat mass. MSC-TG potentially provides a targeted relationship with future child adiposity that is specific to adipose tissue rather than weight-based measures of adiposity. This is further demonstrated by MSC-TG more robustly predicting child FM% at 4 to 6 years, relative to other established neonatal predictors (i.e., birth weight, FM% at birth), explaining 13% of the variance of *in vivo* adiposity in childhood.

These results support the relevance and predictive utility of MSCs collected at birth for *in vivo* phenotypes in childhood. The propensity for fat accumulation in metabolic tissues from the mesodermal lineage may be an important risk factor for susceptibility for childhood obesity and metabolic disease. Assessment of infant umbilical cord MSCs in future studies will support our mechanistic understanding of the fetal origins of cardiometabolic disease and they may serve as a useful surrogate end point for prenatal interventions aimed at reducing future childhood overweight and obesity.O

AUTHOR CONTRIBUTIONS

Allison M. Duensing and Kristen E. Boyle conceived this project. Allison M. Duensing, Madeline Rose Keleher, and Kristen E. Boyle performed the experiments. Lauren E. Gyllenhammer, Allison M. Duensing, and Kristen E. Boyle analyzed the data, interpreted the results, and drafted the manuscript. Katerina Kechris assisted with statistical analyses. Dana Dabelea conceptualized and implemented the parent Healthy Start study. All authors edited the manuscript and approved the final version of the manuscript. Kristen E. Boyle is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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