Influence of Maternal Exercise on Glucose and Lipid Metabolism in Offspring Stem Cells: ENHANCED by Mom. J Clin Endocrinol Metab. 2022 Jul 13;107(8):e3353-e3365

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ABSTRACT

Modern preclinical studies have suggested that during pregnancy, exercise may enhance the metabolic phenotype of both mother and developing offspring, although human progeny studies are still lacking.

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Introduction

The emerging modern and sedentary lifestyle along with the western diet play an important role in the prevalence of diabetes type 2, obesity, various metabolic syndromes, and cardiovascular diseases. Defects in substrate metabolism in peripheral tissue have stimulated such diseases that appear clinically in the variety of conditions including glucose intolerance, hyperlipidemia and insulin resistivity.

Exercise- based interventions have been successful in battling metabolic disorders and their clinical implications by improving substrate metabolism. Recent research suggests that exercising during pregnancy benefits the foetus by reducing the foetus' susceptibility to obesity and other metabolic disorders (1–6). The best and effective method for combatting chronic diseases is aerobic exercise. Evidences also suggest that maternal exercise during pregnancy can improve the health trajectory of both mother and child in both animal models and human case studies (7–9). Exercise during pregnancy therefore protects the offspring from developing metabolic disorders in later life. However, the mechanisms regulating the metabolic health in the offspring, post maternal exercise in humans are not completely understood.

Studies on rodents have shown that offspring of females who were engaged in aerobic exercise during pregnancy increased insulin sensitivity and thus glucose metabolism across the body, it might be possible that the resultant phenotype is programmed in offspring's mesenchymal stromal cells MSCs are cell type and tissue-specific (10–12).

The present study has examined the expanded MSCs from umbilical cord of offspring born to mothers who either performed aerobic exercise (AE-MSCs) or remained inactive (CTRL-MSCs) throughout the pregnancy to overcome this gap. Although skeletal muscle biopsies are a perfect model to analyse the glucose metabolism, it is impractical to have it in infants, which creates a challenge for research on the impact of maternal activity on metabolic programming of foetus in human skeletal muscle.

Although the MSC model employed in the current work is not derived from peripheral tissue that affects an infant's metabolism before or after birth, intrauterine exposures also affect the stem cell/MSC phenotypes of the offspring, which may be used to predict the metabolic health of the offspring.

Study design

Methods

All the experimental studies were performed and approved at East Carolina University. Adult healthy females were recruited between the age group of 18 and 35 years in <16 weeks gestation period without chronic diseases. 20 participants were recruited and randomized.Patients were randomly divided into two groups i.e., a control group employing computerised sequencing, or an aerobic activity. The AE group (n = 10) performed 150 minutes of weekly moderate-intensity exercise during pregnancy while the control group (n = 10) attended sessions of normal stretching and relaxing exercises.

MSC Cell culture

MSCs were isolated from Wharton's jelly by standard explant method and differentiated towards myogenic lineage.

Assays

In the undifferentiated (D0) and myogenically differentiated (D21) states, the following parameters were examined.

Insulin – mediated glycogen synthesis

Serum starvation followed by incubation with media containing radioactive glucose in the presence and absence of insulin was used to assess insulin-mediated glycogen production in MSCs.

Insulin signaling

Akt, AktS473, AktT308, GSK-3 β, and GSK-3βS9 antibodies were used to identify total and phosphorylated proteins

along with the insulin signalling cascade in homogenised cell lysates. Expression of all protein values were adjusted to the expression of the protein β -Actin.

Glucose oxidation

Serum starvation was used to measure glucose oxidation, and radioactive glucose was added to the growth medium for MSCs culture. Liquid scintillation counting was used to determine the generation of non oxidised anionic glycolytic metabolites (lactate, pyruvate, and alanine, or NOGM).

Lipid metabolism

Tracer experiments with radiolabelled fatty acids were conducted to assess the impact of maternal aerobic activity on the metabolism of fatty acids in offspring MSCs. Before measuring oxidation, a different group of MSCs was cultured with medium containing palmitate for 24 hours (PALM condition). Their ability to respond to the lipid challenge served as a marker of metabolic flexibility.

Western blot analysis

MSCs at D0 or D21 for markers of myogenesis (α-actinin 2/ muscle actin ,MyoD) and markers of cell metabolism, cell fate, and substrate handling including total β-Catenin, , MyoD, β-Catenin T41/S45, and alpha-actinin 2, mitochondrial oxidative.

Statistical analysis

Statistical Analysis were carried out using 2-way repeated measures ANOVA or t-tests.

Results

Following conclusions were derived from this study:

1. AE-MSCs at D0 produced less NOGM i.e non-oxidized glucose metabolite and showed a higher fold-change in glycogen synthesis stimulated by insulin over basal levels.
2. In comparison to the control group, AE-MSCs showed significantly higher insulin-mediated glycogen synthesis at D21.
3. For fatty acid metabolism, maternal aerobic exercise has no impact on MSCs. No differences were observed between the groups in complete or incomplete fatty acid oxidation, total fatty acid uptake and fatty acid accumulation at D0. There were no variations in any parameter of fatty acid metabolism at D21.
4. The insulin- stimulated phosphorylation proteins i.e. Akt and GSK-3β were similar at (D0) & (D21) which indicated improvements in insulin-mediated glycogen synthesis at D0 occurred independent of changes in insulin signaling. Other pathways of the insulin signaling were altered in the AE group.
5. Maternal exercise increased mitochondrial biogenesis and enhanced oxidative capability in heart, liver, and skeletal muscle of offspring.
6. Despite the fact that the AE-MSCs synthesis of NOGMs was greatly reduced, they showed a trend toward increased glucose partitioning for oxidation
7. In AE-MSCs expression of complex I at D21 was increased. At D0 and D21, basal and palmitate-stimulated lipid metabolism was comparable between groups.

Implications

The study showed, maternal aerobic exercise enhanced the glucose partitioning toward oxidation (CO2: NOGM). Therefore, according to current findings, maternal aerobic exercise can affect tissue metabolism which suggested that maternal movements may be programmed in humans with certain aspects of the offspring's metabolic phenotype.

The above study provided evidence that human offspring with maternal AE during pregnancy have a programmed metabolic phenotype.

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