Boletín Médico del
Hospital Infantil de México

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REVIEW ARTICLE

Influence of maternal obesity on the skeletal muscle of offspring

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Abstract

Maternal obesity has been described as a clinical entity associated with an increased incidence of metabolic diseases in the offspring, indicating a fetal programming phenomenon during this critical development period. Fetal exposure to an obesogenic environment affects multiple organs and tissues, including skeletal muscle, which is particularly susceptible to stressors from the external environment. Several studies have described alterations in the morphology and composition of skeletal muscle tissue secondary to obesogenic exposure in utero. In addition, modifications in signaling pathways related to the metabolism of energy substrates have been found in children born to mothers with obesity during pregnancy. This review addresses the current evidence describing the consequences of fetal exposure to an obesogenic maternal diet on skeletal muscle tissue, focusing on changes in tissue composition, alterations in signaling pathways related to glucose and fatty acid metabolism, mitochondrial biogenesis, and oxidative phosphorylation.

Keywords: *Maternal obesity. Skeletal muscle. Fetal development. Pregnancy. High-fat diet.*

Influencia de la obesidad materna sobre el músculo esquelético de la progenie

Resumen

La obesidad materna se ha descrito como una entidad clínica asociada con el aumento en la incidencia de enfermedades metabólicas en el producto de la gestación, lo que indica la existencia de un fenómeno de programación fetal que se lleva a cabo durante este periodo crítico del desarrollo. La exposición del feto a un ambiente obesogénico afecta múltiples órganos y tejidos, incluyendo el músculo esquelético, el cual es particularmente susceptible a estresores del ambiente externo. Diversos estudios han descrito alteraciones en la morfología y composición del tejido muscular esquelético secundarias a una exposición obesogénica in utero. Además, se han encontrado modificaciones en vías de señalización relacionadas al metabolismo de sustratos energéticos en los productos de madres con obesidad durante la gestación. En la presente revisión se aborda la evidencia actual que describe las consecuencias de la exposición fetal a una dieta materna obesogénica sobre el tejido muscular esquelético, con especial enfoque en los cambios en la composición del tejido, las alteraciones en las vías de señalización relacionadas con el metabolismo de la glucosa y los ácidos grasos, así como la biogénesis mitocondrial y la fosforilación oxidativa.

Palabras clave: *Obesidad materna. Músculo esquelético. Desarrollo fetal. Embarazo. Dieta alta en grasas.*

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Date of reception: 04-11-2021
Date of acceptance: 21-01-2022
DOI: 10.24875/BMHIM.21000217

Available online: 19-10-2022
Bol Med Hosp Infant Mex. 2022;79(5):284-292
www.bmhim.com

Introduction

Obesity has been increasing worldwide and constitutes a significant public health problem since it favors the development of several comorbidities[1].

Studies in the United States have reported that over 60% of women of reproductive age are overweight at conception, and approximately 30% are obese. In Mexico, obesity prevalence has increased from 32.4% in 2012 to 36.1% in 2018, more prevalent in women (40.2%) and reaching up to 38.5% in women of reproductive age (20-49 years)[2]. This prevalence is relevant as a significant population of infants will be exposed to an obesogenic environment during critical prenatal development[3,4].

Several epidemiological studies and experimental models have argued that maternal health and nutritional status during pregnancy and lactation play critical roles in the programming of neural circuits that regulate the energy balance and behavior of their offspring[5-11]. Furthermore, it has been described that the progeny of obese mothers shows an increased incidence of hypertension, dyslipidemia, hepatic inflammation, obesity, and leptin and insulin resistance, increasing the risk of metabolic syndrome[4,6,12].

In most studies, obesity in animal models is induced by a high-fat diet, as the dietary fat content is considered one of the main factors responsible for increased adiposity. In rodents and humans, a relationship has been demonstrated between the level of dietary fat consumed and body weight or fat gain, and a positive correlation between the amount of consumed fat and the incidence of obesity. Therefore, dietary fat may be the main component responsible for the induction of an obese phenotype[13-16].

The Developmental Origins of Health and Disease hypothesis postulates that exposure to environmental challenges during critical periods of development leads to fetal adaptations that become maladaptive when exposed to environmental and metabolic stressors[17]. Because of this phenomenon, several systems appear to be sensitive to fetal programming[5].

Skeletal muscle represents about 40% of total body mass and is a prominent regulator of glucose and fatty acid metabolism[18]. The early programming of skeletal muscle is relevant, given its capacity to generate metabolic adaptations that can regulate its functionality, performance, and strength. In addition, the metabolism of energy substrates in the skeletal muscle is a crucial element in homeostasis[19]. The intrauterine environment has been described as a critical determinant of muscle mass[20]. Evidence has shown that the involvement of skeletal muscle at an early age is crucial because low muscle mass and strength can contribute to adverse outcomes from early developmental stages, even as early as infancy[21]. This evidence has established maternal obesity as a model for inducing skeletal muscle damage in several animal models[22].

This review addresses the current evidence describing the consequences of fetal exposure to an obesogenic maternal diet on skeletal muscle tissue, focusing on changes in tissue composition, alterations in signaling pathways related to glucose and fatty acid metabolism, mitochondrial biogenesis, and oxidative phosphorylation. It should be mentioned that obesogenic diets differ among studies. Typically, diets containing > 30% of total energy as fat lead to the development of obesity[23]; however, obesity has been induced in animals with fat-containing diets as low as 13% of total energy[24] or as high as 85%[25]. Diet-induced obesity (DIO) models consist of diets with a variable fat content (% kcal of fat). The most commonly used DIO models range from 45% to 60% of fat content[16].

Although the obesogenic diets in the studies reviewed here are heterogeneous, the obese maternal phenotype secondary to the administration of the obesogenic diet during gestation has been demonstrated, confirming that the fetus is exposed to this maternal phenotype. Finally, on the content of other macronutrients in the diets, some authors have discussed a positive relationship between the level of fat in the diet and the degree of obesity, even without controlling for the amount of protein in the diet[23]. This relationship suggests that, although other macronutrients, such as protein, are relevant in skeletal muscle composition, the maternal obese phenotype associated with the consumption of a high-fat diet may be sufficient to induce changes in the skeletal muscle of the offspring, regardless of the unfortunately underestimated protein content of the diets mentioned in the reviewed studies.

Impact of a maternal high-fat and high-carbohydrate diet on the skeletal muscle of the offspring

The number of muscle fibers is partially determined since prenatal development. After birth, muscle fibers may undergo a process of hypertrophy, but hyperplasia occurs to a lesser extent; therefore, effects on muscle development during the embryonic and fetal periods may generate deleterious effects in postnatal life[21]. An inadequate nutrient supply during prenatal development can lead to impaired muscle development in the product, resulting in reduced muscle mass and function in postnatal life (Table 1). This effect has been

Table 1. Effects of maternal obesogenic diet on skeletal muscle morphology and function in offspring

Animal model	Maternal diet	Muscle	Age	Effect on the progeny	Ref
Mouse	High-fat diet (45% kcal from fat)	Tibialis anterior	15 weeks after birth	Lower muscle weight	26
Mouse	Sucrose-rich diet (26% simple sugars, 5% fat, 12% protein w/w)	Tibialis anterior	3 months after birth	Reduction in muscle mass	27
Rat	High-fat diet with fast-absorbing carbohydrates [protein 24.2 g, fat 20.5 g, carbohydrates 49.4 g/100 g diet (carbohydrates: 81.9% sucrose, 18.1% fructooligosaccharides w/w)]	Gastrocnemius	3 and 7 weeks after birth	Decrease in muscle weight	19
Rat	High-fat diet with fast-absorbing carbohydrates [protein 24.2 g, fat 20.5 g, carbohydrates 49.4 g/100 g diet (carbohydrates: 81.9% sucrose, 18.1% fructooligosaccharides w/w)]	Extensor digitorium longus and tibialis	7 weeks after birth	Decrease in muscles weight	19
Rat	High-fat diet (45% kcal from fat, 20% kcal from protein, 35% kcal from carbohydrates)	Gastrocnemius	150 days after birth	Decrease in total protein content in muscle	28
Mouse	High-fat diet (45% kcal from fat)	Gastrocnemius	20 weeks after birth	Increase in muscle triglyceride content	29
Non-human primate	Western diet (37% kcal from fat)	Gastrocnemius	Gestational day 130	Decrease in intramuscular triglycerides, increase in fatty acids and intramyocellular phospholipids	30
Mouse	High-fat diet (40% kcal from fat, 23% kcal from protein, 37% kcal from carbohydrates)	—	From 7 to 25 weeks after birth	Decrease in the capacity to resist voluntary exercise	18
Mouse	High-fat diet (40.2% kcal from fat, 23% kcal from protein, 36.8% kcal from carbohydrates)	—	From 4 weeks after birth	Reduced exercise performance and reduced physical training efficiency	20
Mouse	Sucrose-rich diet (26% simple sugars, 5% fat, 12% protein w/w)	—	3 months after birth	Reduction in locomotor activity	27

Ref: reference.

evidenced in a murine model of mothers on a high-fat diet, in which the progeny showed a reduced weight of the tibialis anterior muscle at 15 weeks after birth[26].

Several studies have demonstrated the effects of a high-sugar maternal diet on the offspring. Samuelsson et al.[27] showed a reduction in tibialis anterior muscle mass in female offspring in a murine model of mothers fed a high-sugar diet. Meanwhile, Salto et al.[19] observed that a high-fat maternal diet with fast-absorbing carbohydrates significantly decreased gastrocnemius muscle weight in the offspring. In contrast, this effect was not observed with a high-fat diet with slow-absorbing carbohydrates. This finding was observed at early and late stages after birth, indicating a long-term decline in muscle mass. Interestingly, at a later stage (7 weeks after birth), the offspring also showed a reduction in muscle weight of both the extensor digitorum longus and the tibialis anterior muscles[19].

In addition to a decrease in skeletal muscle weight, other changes in muscle composition have been described. For example, a reduction of total protein content in the gastrocnemius muscle was observed in a murine model in response to exposure to an obesogenic environment *in utero*[28]. Modifications in lipid content in this muscle characterized by an increase in triglycerides were also identified[29]. Similarly, in a non-human primate animal model, a Western diet before and during pregnancy induced a decrease in intramuscular triglycerides in the offspring but an increase in fatty acids and intramyocellular phospholipids[30].

Along with the alterations in skeletal muscle composition, the progeny of mothers fed a high-fat or

high-sugar diet show a decreased capacity for voluntary exercise endurance[18], a significant reduction in exercise performance, low efficiency in physical training[20], and reduced locomotor activity[27], indicating functional alterations in skeletal muscle due to the obesogenic environment.

An obesogenic maternal diet and alterations in carbohydrate and lipid metabolism in the skeletal muscle of the offspring

The relevance of maternal programming in skeletal muscle, carbohydrate, and lipid metabolism has been shown in several studies (Table 2). In a Japanese macaque model of offspring from mothers fed a high-fat diet, a decrease in insulin-induced glucose uptake was observed in the rectus femoris and soleus muscles, which was a long-term effect. The effect was also found in the rectus femoris muscle; IRS1 (insulin receptor substrate 1) and p110α (phosphoinositide 3-kinase subunit) content decreased in fetal muscles, along with a subsequent decrease in IRS1 phosphorylation during adolescence. Authors also showed a reduction in insulin-stimulated phosphorylation of Akt (also known as protein kinase B) downstream of insulin receptor activation[17]. Another study in a murine model demonstrated that the offspring of obese mothers showed decreased IRS1 phosphorylation in skeletal muscle[31]. In the offspring of mothers fed a high-fat diet with fast-absorbing carbohydrates, a decrease in Akt phosphorylation was also observed in both early and late stages[19]. These same effects were demonstrated when the mothers were fed only a high-fat diet[31].

Other models have found increased Akt protein levels but reduced phosphorylation at the Ser473 position, indicating that there could be a compensatory mechanism evidenced by increased Akt protein expression due to its reduced activation[32]. Notably, some insulin signaling cascades and glucose uptake changes do not occur in exacerbated adiposity, hyperinsulinemia, or systemic insulin resistance, suggesting that alterations in insulin-mediated signaling may be elicited before systemic effects[17].

Alterations in the insulin-mediated signaling pathway may be reflected in a decreased skeletal muscle glucose uptake capacity. Murine offspring of obese mothers show decreased expression of GLUT4 (glucose transporter type 4) in skeletal muscle[33,34]. This diminished GLUT4 expression could be due to deficient insulin-mediated signaling. In a sheep model in which dams were fed a hypercaloric diet, the skeletal muscle of the offspring showed high GLUT4 mRNA expression, whereas protein expression of this molecule was decreased. The authors proposed that the increased expression of the *GLUT4* gene transcript could compensate for the reduced protein level[35].

Similarly, alterations in other molecules involved in insulin signaling have been described. In a sheep model, a higher expression of GSK3α (glycogen synthase kinase 3) accompanied by a decreased phosphorylation of GSK3α at the Ser21 position was observed in the skeletal muscle offspring of mothers fed a hypercaloric diet. As GSK3α is a negative modulator of insulin actions, a decrease in the activity of this molecule could be related to abnormal insulin-mediated glucose metabolism[35]. De Fante et al.[31] conducted a study in murine offspring from a maternal obesity model and observed increased expression of p-JNK (phospho-c-Jun N-terminal kinase), p-IKK (phospho-IκB kinase), PTP1B (protein-tyrosine phosphatase 1B), and PEPCK (phosphoenolpyruvate carboxykinase) in the soleus muscle. Increased expression of PTP1B has been associated with an attenuation of insulin-mediated signaling, and PEPCK is an enzyme involved in gluconeogenesis.

In addition, lower expression of the AdipoR1 (adiponectin receptor 1) transcript was observed in offspring exposed to a high-fat maternal diet, suggesting a dysfunction in the signaling of this adipokine in the skeletal muscle, which could contribute to insulin resistance and obesity in postnatal life[34]. The maternal obesogenic environment also induces a decrease in the phosphorylation levels of AMPK (AMP-activated protein kinase), a kinase associated with muscle energy status, and a reduction in the phosphorylation levels of mTOR (mammalian target of rapamycin)[19]. Furthermore, other modifications have also been found in the expression of molecules such as Cox4 (cytochrome c oxidase subunit 4) and Cyt (cytochrome) genes involved in energy metabolism[36].

As for other parameters related to the metabolism of energy substrates, some studies found that the offspring of obese mothers preferentially use glucose as an energy source, even despite alterations in the insulin-signaling pathway. In a murine model of dams fed a high-fat and fast-digesting carbohydrates diet, the skeletal muscle of the offspring showed increased expression of PKM2 (pyruvate kinase muscle isozyme), indicating an increased dependence on glucose for energy[19]. In other *in vivo* models, a significantly decreased expression of CD36 and FAS mRNA (essential for fatty acid metabolism, and GLUT1 (glucose transporter type 1, a transporter for basal glucose uptake) was observed in the quadriceps muscle of offspring in a model of obesity[20].

However, the preference of offspring skeletal muscle to utilize lipid substrates has also been evidenced. In

Table 2. Effects of maternal obesogenic diet on carbohydrate and lipid metabolism in offspring skeletal muscle

Animal model	Maternal diet	Muscle	Age	Effect on the progeny	Ref
Japanese macaque	High-fat diet (36.6% kcal from fat)	Rectus femoris and soleus	Gestational day 130	Decreased insulin-induced glucose uptake in fetal muscles	17
Japanese macaque	High-fat diet (36.6% kcal from fat)	Soleus	14 months after birth	Decreased insulin-induced glucose uptake in muscle	17
Japanese macaque	High-fat diet (36.6% kcal from fat)	Rectus femoris	Gestational day 130	Decreased IRS1 and p110α (PI3K subunit) in the fetal muscle	17
Japanese macaque	High-fat diet (36.6% kcal from fat)	Rectus femoris	Gestational day 130	Decreased insulin-stimulated Akt phosphorylation in fetal muscle	17
Japanese macaque	High-fat diet (36.6% kcal from fat)	Soleus	14 months after birth	Decreased insulin-stimulated Akt and IRS1 phosphorylation in muscle	17
Rat	High-fat diet with fast-absorbing carbohydrates [protein 24.2 g, fat 20.5 g, carbohydrates 49.4 g/100 g diet (carbohydrates: 81.9% sucrose, 18.1% fructooligosaccharides w/w)]	Gastrocnemius	3 and 7 weeks after birth	Decreased Akt phosphorylation in muscle	19
Mouse	High-fat diet (protein 20.8 g, fat 23.6 g, carbohydrates 41.2 g/100 g diet)	Soleus	28 days after birth	Decreased Akt and IRS1 phosphorylation in muscle	31
Mouse	High-fat diet (protein 20.8 g, fat 23.6 g, carbohydrates 41.2 g/100 g diet)	Soleus	82 days after birth	Decreased insulin-induced Akt and IRS1 phosphorylation in muscle	31
Mouse	High-fat diet (protein 20.8 g, fat 23.6 g, carbohydrates 41.2 g/100 g diet)	Soleus	28 days after birth	Increased p-JNK, p-IKK, and PTP1B expression	31
Mouse	High-fat diet (protein 20.8 g, fat 23.6 g, carbohydrates 41.2 g/100 g diet)	Soleus	82 days after birth	Increased p-IKK expression	31
Mouse	High-fat diet (protein 20.8 g, fat 23.6 g, carbohydrates 41.2 g/100 g diet)	Soleus	82 days after birth	Increased insulin-induced PTP1B and PEPCK expression	31
Rat	High-fat and sucrose diet (23.5% total fat, 9.83% saturated fat, 20% sucrose, 23.3% protein w/w)	Soleus	12 months after birth	Increased Akt total protein, reduction in the levels of phosphorylation at position Ser473	32
Rat	High-fat diet (23-36% fat, 19.4% protein, 44.9-40% carbohydrate w/w)	Gastrocnemius	19 days after birth	Decreased mRNA expression of GLUT4 in muscle	33
Rat	High-fat diet (15% fat, 18.9% casein, 0.3% l-cysteine, 48.3% corn starch, 3.3% maltodextrin, 13% sucrose, 4.7% cellulose, 4.3% mineral mix, 1.1% vitamin mix w/w)	Soleus	3 and 8 weeks after birth	Decreased mRNA and protein expression of GLUT4 in muscle	34
Sheep	Hypercaloric diet (170-190% high metabolizable energy requirements)	Quadriceps	4 months after birth	Increased expression of GLUT4 mRNA, decreased protein expression of GLUT4 in muscle	35
Sheep	Hypercaloric diet (170-190% high metabolizable energy requirements)	Quadriceps	4 months after birth	Increased GSK3α protein expression and decreased phosphorylation of GSK3α at the Ser21 position	35
Rat	High-fat diet (15% fat, 18.9% casein, 0.3% l-cysteine, 48.3% corn starch, 3.3% maltodextrin, 13% sucrose, 4.7% cellulose, 4.3% mineral mix, 1.1% vitamin mix w/w)	Soleus	3 and 8 weeks after birth	Decreased mRNA expression of AdipoR1 in muscle	34
Rat	High-fat diet with fast-absorbing carbohydrates [protein 24.2 g, fat 20.5 g, carbohydrates 49.4 g/100 g diet (carbohydrates: 81.9% sucrose, 18.1% fructooligosaccharides w/w)]	Gastrocnemius	3 weeks after birth	Decrease in the levels of AMPK phosphorylation in muscle	19

(continues...)

Table 2. Effects of maternal obesogenic diet on carbohydrate and lipid metabolism in offspring skeletal muscle *(continued)*

Animal model	Maternal diet	Muscle	Age	Effect on the progeny	Ref
Rat	High-fat diet with fast-absorbing carbohydrates [protein 24.2 g, fat 20.5 g, carbohydrates 49.4 g/100 g diet (carbohydrates: 81.9% sucrose, 18.1% fructooligosaccharides w/w)]	Gastrocnemius	7 weeks after birth	Decrease in the levels of mTOR phosphorylation in muscle	19
Mouse	High-fat diet (60% kcal from fat)	Quadriceps	12 months after birth	Decreased Co×4 and Cytc mRNA expression	36
Rat	High-fat diet with fast-absorbing carbohydrates [protein 24.2 g, fat 20.5 g, carbohydrates 49.4 g/100 g diet (carbohydrates: 81.9% sucrose, 18.1% fructooligosaccharides w/w)]	Gastrocnemius	7 weeks after birth	Increased expression of PKM2	19
Mouse	High-fat diet (40.2% kcal from fat, 23% kcal from protein, 36.8% kcal from carbohydrates)	Quadriceps	12 weeks after birth	Decreased levels of CD36 and FAS mRNA in the muscle	20
Mouse	High-fat diet (40.2% kcal from fat, 23% kcal from protein, 36.8% kcal from carbohydrates)	Quadriceps	12 weeks after birth	Decreased mRNA expression of GLUT1 in muscle	20
Non-human primate	Western diet (37% kcal from fat)	Gastrocnemius	Gestational day 130	Increased protein expression of CPT-1β and VLCAD. Decreased protein expression of SCHAD	30
Non-human primate	Western diet (37% kcal from fat)	Gastrocnemius	Gestational day 130	Increased mRNA expression of PDK4	30
Non-human primate	Western diet (37% kcal from fat)	Gastrocnemius	Gestational day 130	Increase in lipidic peroxidation in muscle.	30
Non-human primat	Western diet (37% kcal from fat)	Gastrocnemius	Gestational day 130	Increased expression of 4HNE-modified proteins in muscle	30

AdipoR1: adiponectin receptor 1; Akt: protein kinase B; AMPK: AMP-activated protein kinase; Co×4: cytochrome C oxidase subunit 4; CPT-1β: carnitine palmitoyl transferase 1β; Cyt: cytochrome; GLUT1: glucose transporter type 1; GLUT4: glucose transporter type 4; GSK3α: glycogen synthase kinase 3; IRS1: insulin receptor substrate 1; mTOR: mammalian target of rapamycin; p-JNK: phospho-c-Jun N-terminal kinase; p-IKK: phospho-IκB kinase; PDK4: pyruvate dehydrogenase kinase 4; PEPCK: phosphoenolpyruvate carboxykinase; PI3K: phosphoinositide 3-kinase subunit; PKM2: pyruvate kinase muscle isozyme; PTP1B: protein-tyrosine phosphatase 1B; SCHAD: short-chain 3-hydroxy acyl-CoA dehydrogenase; VLCAD: very long-chain acyl-CoA dehydrogenase.

non-human primates whose mothers were fed a Western diet, CPT-1β (carnitine palmitoyl transferase 1β) protein, a rate-limiting enzyme for oxidation of long-chain fatty acids, increased to 2-fold in the skeletal muscle of the offspring. Similarly, the expression of the *PDK4* (pyruvate dehydrogenase kinase 4) gene and VLCAD (very-long-chain acyl CoA dehydrogenase) protein, specific for long-chain fatty acid oxidation, increased. In contrast, SCHAD (short-chain 3-hydroxy acyl-CoA dehydrogenase) protein expression decreased. Furthermore, increased fetal muscle lipid peroxidation along with increased 4HNE-modified proteins was found in skeletal muscle in this model[30].

Based on these findings, it is suggested that maternal obesity combined with a Western diet downregulates genes involved in glucose utilization and upregulates the ability of cells to oxidize fatty acids[30].

An obesogenic maternal environment modifies mitochondrial function in the offspring

Mitochondrial function is considered an essential process in skeletal muscle function. Moreover, several studies have shown that obesogenic exposure *in utero* could lead to alterations of this organelle (Table 3).

Maragkoudaki et al.[37] described increased mitochondrial DNA copy number in the skeletal muscle of offspring in a murine model of maternal obesity. Mitochondrial DNA copy number has been described as a determinant of reduced energy expenditure and glucose tolerance in the offspring of obese mothers. Increased mitochondrial genetic material has been related to early exposure to reactive oxygen species in maternal hyperinsulinemia secondary to obesity and could reflect a compensatory

Table 3. Effects of maternal obesogenic diet on mitochondrial function in offspring skeletal muscle

Animal model	Maternal diet	Muscle	Age	Effect on the progeny	Ref
Mouse	High-fat diet (16% fat, 33% simple sugars, 15% protein)	Tibialis anterior	30 days after birth	Increased number of copies of mitochondrial DNA in muscle	37
Rat	Hypercaloric diet (40% excess calories, 220 kcal/kg/day)	Gastrocnemius	130 days after birth	Reduced mRNA expression of PGC1α, SIRT1, and Mfn1	38
Non-human primate	Western diet (37% kcal from fat)	Gastrocnemius	Gestational day 130	Increased mRNA expression of GADD45, SIRT3, UCP2, and UCP3 in muscle	30
Mouse	High-fat diet (40% kcal from fat, 23% kcal from protein, 37% kcal from carbohydrates)	Quadriceps	25 weeks after birth	Decreased protein expression of the oxidative phosphorylation complex I in muscle	18
Rat	High-fat and sucrose diet (23.5% total fat, 9.83% saturated fat, 20% sucrose, 23.3% protein w/w)	Soleus	12 months after birth	Decreased protein expression of the oxidative phosphorylation complexes I, II, and V in muscle	32
Non-human primate	Western diet (37% kcal from fat)	Gastrocnemius	Gestational day 130	Increased activity of the oxidative phosphorylation complexes I and IV. Increased expression of ATP synthase subunits ATP5C1 and ATP5A1 in muscle	30
Non-human primate	Western diet (37% kcal from fat)	Gastrocnemius	Gestational day 130	Decreased activity of the citrate synthase in muscle	30
Non-human primate	Western diet (37% kcal from fat)	Gastrocnemius	Gestational day 130	Decreased mitochondrial/nuclear DNA ratio in muscle	30

GADD45: growth arrest and DNA damage; Mfn1: mitofusin 1; PGC1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SIRT1: sirtuin 1; SIRT3, sirtuin 3; UCP2: uncoupling protein 2; UCP3: uncoupling protein 3.

mechanism responding to decreased mitochondrial function. In addition, it has been proposed that increased mitochondrial DNA could reflect a maladaptive response and lead to a non-functional response to oxidative stress and maternal hyperglycemia.

Decreased expression of PGC1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha), a transcriptional regulator related to energy metabolism and mitochondrial biogenesis, SIRT1 (sirtuin 1) and Mfn1 (mitofusin 1), both involved in the mitochondrial repair process in the muscle, has been described in the offspring of a murine model of maternal obesity[38].

Moreover, other alterations related to oxidative stress and mitochondrial function have been reported. A significantly increased expression of the gene encoding the GADD45 (growth arrest and DNA damage) protein, a marker of cellular stress, was described in a non-human primate model, along with an increased expression of SIRT3 (sirtuin 3), a mitochondrial protein associated with the induction of the antioxidant system. Increased expression of the uncoupling proteins UCP2 (uncoupling protein 2) and UCP3 (uncoupling protein 3), which have been associated with increased fatty acid oxidation in murine models, was also found. These data suggest that the Western obesogenic maternal diet increases the production of reactive oxygen species and activates signaling pathways responsible for protection against cellular stress in fetal muscle[30].

Other studies in animal models have shown mitochondrial alterations related to oxidative phosphorylation, an essential function in skeletal muscle metabolism. Reduced complex I of the electron transport chain has been observed in the offspring of a murine model of maternal obesity with a high-fat diet, indicating that this condition attenuates the ability to generate a proton gradient necessary for ATP synthesis. This process is critical during endurance exercise and could explain the altered muscle performance[18,32].

Similarly, decreased protein expression of complexes II and V has been found in another model of maternal obesity, which also suggests a reduction in mitochondrial function and ATP production. This mechanism could contribute to the development of insulin resistance and lead to increased generation of reactive oxygen species, lipid peroxidation, and release of proinflammatory cytokines[32].

Conversely, in non-human primates, an increase in the activity of complexes I and IV of the oxidative

phosphorylation chain together with an increased expression of ATP synthase subunits, was found in the skeletal muscle of the offspring of obese mothers fed a Western diet. Interestingly, despite the increased activity of specific electron transport chain components, a decrease in citrate synthase activity was observed, while the mitochondrial/nuclear DNA ratio was up to 2-fold lower in the offspring of obese mothers fed a Western diet. Despite the increased activity of the complexes, the efficiency of electron transport chain coupling was significantly lower in the offspring of obese mothers fed a Western diet[30].

In conclusion, maternal obesity has been postulated as an inducer of damage in multiple fetal organs and tissues, including skeletal muscle. Skeletal muscle has movement and locomotion functions and, in parallel, plays a vital role in the metabolism of energy substrates. Given its multiple functions, the secondary consequences of exposure to an obesogenic environment *in utero* could severely impact postnatal life.

As described in this review, maternal obesity induces changes in skeletal muscle morphology and composition, which affect physical performance. In addition, exposure to an obesogenic diet induces alterations in carbohydrate and lipid metabolism. Changes in the signaling pathway of insulin receptors involved in glucose uptake by tissues, as well as modifications in the utilization of fatty acids as a source of energy, are prominent. Interestingly, some studies have proposed the existence of compensatory mechanisms generated to counteract the deleterious effects of maternal obesity in the offspring, highlighting the plasticity of skeletal muscle tissue and its capacity to create adaptive responses to external stressors.

Fetal programming is a complex process in which multiple factors are involved. Questions about the causal mechanisms of this phenomenon and the magnitude of the effects produced by fetal exposure to an obesogenic environment in prenatal life remain unanswered. Undoubtedly, in the future, there will be proposals to help explain this phenomenon and approaches to counteract and prevent the deleterious effects of maternal obesity on the offspring.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflict of interest.

Funding

No funding.

Acknowledgments

Ana Luisa Álvarez-Chávez received a National Research Assistant Level 3, Consejo Nacional de Ciencia y Tecnología (CONACyT) Mexico fellowship award.

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