Research Article

Maternal Moderate Physical Training during Pregnancy Attenuates the Effects of a Low-Protein Diet on the Impaired Secretion of Insulin in Rats: Potential Role for Compensation of Insulin Resistance and Preventing Gestational Diabetes Mellitus

Carol Góis Leandro,1,2 Marco Fidalgo,2 Adriano Bento-Santos,3 Filippe Falcão-Tebas,2 Diogo Vasconcelos,4 Raul Manhães-de-Castro,1,3 Angelo Rafael Carpinelli,4 Sandro Massao Hirabara,4,5 and Rui Curi4

1 Department of Nutrition, Federal University of Pernambuco, 50670-901 Recife, PE, Brazil
2 Department of Physical Education and Sports Science, CA V, Federal University of Pernambuco, 55608-680 Recife, PE, Brazil
3 Department of Neuropsychiatry and Behavioral Science, Federal University of Pernambuco, 50670-420 Recife, PE, Brazil
4 Institute of Biomedical Science, University of São Paulo, 05508-000 São Paulo, SP, Brazil
5 Institute of Physical Activity Sciences and Sports, Cruzeiro do Sul University, 01506-000 São Paulo, SP, Brazil

Correspondence should be addressed to Carol Góis Leandro, carolleandro22@gmail.com

Received 14 June 2012; Revised 16 July 2012; Accepted 18 July 2012

Academic Editor: Renata Gorjão

Copyright © 2012 Carol Góis Leandro et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The effects of pregestational and gestational low-to-moderate physical training on insulin secretion in undernourished mothers were evaluated. Virgin female Wistar rats were divided into four groups as follows: control (C, n = 5); trained (T, n = 5); low-protein diet (LP, n = 5); trained with a low-protein diet (T + LP, n = 5). Trained rats ran on a treadmill over a period of 4 weeks before mate (5 days week−1 and 60 min day−1, at 65% of VO2max). At pregnancy, the intensity and duration of the exercise were reduced. Low-protein groups were provided with an 8% casein diet, and controls were provided with a 17% casein diet. At third day after delivery, mothers and pups were killed and islets were isolated by collagenase digestion of pancreas and incubated for a further 1 h with medium containing 5.6 or 16.7 mM glucose. T mothers showed increased insulin secretion by isolated islets incubated with 16.7 mM glucose, whereas LP group showed reduced secretion of insulin by isolated islets when compared with both C and LP + T groups. Physical training before and during pregnancy attenuated the effects of a low-protein diet on the secretion of insulin, suggesting a potential role for compensation of insulin resistance and preventing gestational diabetes mellitus.

1. Introduction

Pregnancy requires an increase in insulin secretion-induced glucose metabolism, in order to compensate for the insulin resistance at the end of gestation [1]. In pregnant rats, the threshold of glucose-stimulated insulin secretion begins to diverge from controls by day 10 and islet cell proliferation and insulin secretory profiles are inhibited by day 20 to avoid gestational diabetes [2]. Return to normal values of insulin secretion and inhibition of cell division is particularly important when the adequate nutrient intake is not provided during pregnancy. For example, maternal low-protein diet (6% casein) causes a loss of glucose sensitivity and secretory capacity in pancreatic islets, which is probably the result of alterations to the coupling of stimuli with insulin secretion [3]. In fact, a maternal low-protein diet decreases insulin secretion and impairs glucose homeostasis, leading to gestational diabetes mellitus and increased risk of chronic diseases in later life [1, 4].

Recently, it has been recognized that an active maternal lifestyle, including regular to moderate physical activity, improves aerobic fitness and the maternal-fetal physiological
reserve by enhancing nutrient and oxygen availability to the fetus [5–7]. Maternal physical activity is associated with normalized body weight gain, enhanced cardiorespiratory, and improved oxidative capacity and insulin sensitivity of skeletal muscle [8]. These physiological benefits mainly occur according to the type and volume of the exercise, physical fitness of the mother, the time point in the pregnancy when the exercise is carried out and also the duration and intensity of the exercise [9, 10]. Physical exercise training has been associated with reduced risk of metabolic disease and enhances both cardiorespiratory and metabolic functions [11–14]. These effects are mainly due to improved oxidative capacity and insulin sensitivity of skeletal muscle, since reduced muscle dysfunction and insulin resistance have been associated to the development of several chronic diseases [15–20]. Exercise is considered moderate intensity when consumption (VO2max). In our previous study, we demonstrated that maternal physical training may protect mothers against maternal undernutrition or overnutrition.

The effects of maternal moderate physical training can be expected modifying glucose metabolism in pregnancy once regular physical activity in nonpregnant individual is known to improve peripheral insulin sensitivity, glucose tolerance, and may aid in preserving β-cell function [11]. Regular practice of moderate exercise has been associated with improved fitness, reduction of body weight, and increased muscle mitochondrial biogenesis and antioxidant defence [5, 23]. Our previous experimental data supports the idea that maternal physical training may protect mothers against perinatal undernutrition environment [21, 24]. Recently, we showed in rats that physical training was able to normalize the effects of a low-protein diet on fasting serum glucose at the second and third weeks of gestation [25]. This differential effect observed in previously active compared with undernourished dams may be related to reduced risk of gestational diabetes mellitus, since an exercise program may improve insulin sensitivity and fasting plasma glucose concentrations of women at risk for gestational diabetes mellitus [26].

Thus, the main goal of this study was to evaluate the impact of a moderate to low intensity protocol of physical training during gestation on the secretion of insulin whose mothers were undernourished. Our hypothesis is that maternal physical training-induced physiological adaptations during gestation attenuate the impact of a perinatal low-protein diet on the secretion of insulin. This is a topic of particular interest as a maternal lifestyle can be considered a therapeutic means of countering the effects of either maternal undernutrition or overnutrition.

2. Methods

Experimental protocol was approved by the Ethical Committee of the Biological Sciences Center, Federal University of Pernambuco, Brazil and followed the Guidelines for the Care and Use of Laboratory Animals [27].

2.1. Animals. Virgin female albino Wistar rats (Rattus norvegicus) aged 60 days and weighting 180 ± 11 g (mean ± S.E.M.) were obtained from the Department of Physiology and Biophysics, Institute of Biomedical Sciences, University of São Paulo, Brazil. Female rats were maintained at a room temperature of 22 ± 1°C and controlled light-dark cycle (dark 6:00 a.m.–6:00 p.m.). The standard laboratory chow for animals (52% carbohydrate, 21% protein, 4% lipids-Nuvilab CR1-Nuvital) and water were given ad libitum. Animals were randomly divided into two groups: untrained rats (NT, n = 10) and trained rats (T, n = 10). Trained rats were submitted to a training program of moderate running over a period of 4 weeks (5 days per week and 60 minutes per day) on a treadmill (Millennium Inbramed, Brazil) at a controlled intensity based on their VO2 max. After a 4-week training period, the rats were mated (2 females for 1 male). The day on which spermatozoa were present in a vaginal smear was designated as the day of conception (day 0 of pregnancy). Pregnant rats were then transferred to individual cages. Half of rats of each group received either 17% casein diet or 8% casein (low-protein group, LP) isocaloric diet ad libitum (Table 1). Thus, two more groups were formed: untrained (C, n = 5), trained (T, n = 5), untrained with low-protein diet (LP, n = 5), and trained with low-protein diet (T + LP, n = 5). Mother’s body weight was weekly determined throughout the experiment. On the time of delivery, the litter size and pup’s birth weight were recorded. The litters of six pups represent the sample that was evaluated: control (C, n = 5); trained (T, n = 5); low-protein diet (LP, n = 5); trained with low-protein diet (T + LP, n = 5). The evaluation of body weight and gain of body weight of pups was recorded until the 3rd d of life with a Marte scale with 100 mg precision. Afterwards, mothers and pups were killed by decapitation.

| Table 1: Composition of the diets (control 17% and low protein 8%) |
|---------------------------------------------------------------|
| **Ingredients** | **Amount for 1 Kg of diet** |
|                 | **Low protein** | **Control** |
| Casein           | 79.3 g         | 179.3 g     |
| Vitamin mix*     | 10 g           | 10 g        |
| Mineral mixture† | 35 g           | 35 g        |
| Cellulose        | 50 g           | 50 g        |
| Bitartrato of choline | 2.5 g     | 2.5 g        |
| DL-methionine    | 3.0 g          | 3.0 g        |
| Soya oil         | 70 mL          | 70 mL       |
| Corn starch      | 750.2 g        | 650.2 g     |

*Vitamin mixture contained the following (mg/kg of diet): retinol, 12; cholecalciferol, 0.125; thiamine, 40; riboflavin, 10; pantothenic acid, 1; menadione, 80; nicotinic acid, 200; choline, 2720; folic acid, 10; p-aminobenzoic acid, 100; biotin, 0.6.
2.2. Protocol of Physical Training. Considering that maternal physical exercise-induced changes depend on intensity, duration, and frequency of effort, our group standardized an experimental protocol of maternal physical training (based on blood lactate concentration and oxygen consumption) [21]. Briefly, rats ran on a treadmill during the four weeks prior to pregnancy (5 days week\(^{-1}\) and 60 min day\(^{-1}\), at 65%\(\text{VO}_2\text{max}\)). The protocol was divided into four progressive stages in each session: (i) warm-up (5 minutes); (ii) intermediary (20 minutes); (iii) training (30 minutes); (iv) cool-down (5 minutes) periods. The percentage of \(\text{VO}_2\text{max}\) during the sessions of training was kept around 55–65% [21]. During pregnancy, rats ran at a progressively lower intensity of effort (40%\(\text{VO}_2\text{max}\), 5 days week\(^{-1}\), and 20 min day\(^{-1}\)) until the 19th day of gestation [21].

2.3. Mother’s Body Weight and Food Intake. Mother’s body weight was daily recorded. Daily food consumption was determined by the difference between the amount of food provided at the onset of the dark cycle (06.00 hours) and the amount of food remaining 24 h later [28]. Body and food weights were recorded with a Marte Scale (AS-1000) with a 0.01-g accuracy.

2.4. Islet Isolation and Insulin Secretion. Islets were isolated from five fasting mothers in each group by collagenase digestion of pancreas followed by separation from pancreatic debris by centrifugation on Ficoll gradients as previously described [29]. Groups of five islets were initially incubated for 45 min at 37°C in Krebs-bicarbonate buffer containing 5.6 mM glucose and equilibrated with 95% \(\text{O}_2/5\% \text{CO}_2\), pH 7.4. The solution was then replaced with fresh Krebs-bicarbonate buffer and the islets were incubated for a further 1 h with medium containing 5.6 or 16.7 mM glucose. The incubation medium contained (in mM): NaCl 115, KCl 5, NaHCO\(_3\) 24, CaCl\(_2\) 2.56, MgCl\(_2\) 1, and BSA 0.3% (w/v). The cumulative insulin release during 1 h was quantified by radioimmunoassay using rat insulin as standard.

2.5. Statistical Analyses. Values are presented as means ± S.E.M. For statistical analysis, data were analyzed by two-way repeated measures ANOVA, with mothers’ diet and physical training as factors. Bonferroni’s post-hoc test was used. Each litter of six pups was considered one sample, and statistical analyses were performed by using the mean values of each litter. Significance was set at \(P < 0.05\). Data analysis was performed using the statistical program Graphpad Prism 5 (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

Body weight was lower in trained rats during the third and fourth weeks pregestation (Figure 1(a)). LP mothers showed a reduction in the body weight when compared to C mothers during gestation (\(P < 0.01\)), whereas physical training had no effect in the body weight (Figure 1(a)).

The number of pups (litter size) born from mothers was similar among groups. Litter weight, birth weight, and body weight in the first three days of life of pups from mothers submitted to a low-protein diet during gestation, trained or not, were lower when compared to control (Table 2).

Trained mothers showed an increase of insulin secretion by isolated islets incubated with stimulatory (16.7 mM) concentration of glucose (Figure 2). However, low-protein diet during gestation induced a reduction in the secretion of insulin by isolated islets when compared with both control and LP + T groups (Figure 2).

4. Discussion

Maternal exercise guidelines preconize that 30 min, at least, of moderate-intensity exercise a day on most, if not all, days of the week is satisfactory for health [8]. Following these recommendations, a controlled prospective studies have demonstrated that moderate pregestational exercise (approximately 50% to 70% of \(\text{VO}_2\text{max}\)) is useful to increase metabolic rate (reduction of body weight) and improve cardiorespiratory fitness and maternal-fetal physiological reserve [30]. In addition, previous study has demonstrated an improved cardiovascular function, limited gain of body weight, and reduced risk of gestational diabetes mellitus and hypertension [31]. In the present study, trained mothers demonstrated reduced body weight in the second and third weeks pregestation, but this normalized throughout gestation. Our results are in agreement with previous studies [21, 24]. It is well established that regular physical exercise increases lean body mass and induces a higher utilisation of fatty acids as fuel by skeletal muscles once the intensity of the exercise is maintained at 65–70% of \(\text{VO}_2\text{max}\) [32].

Maternal physical training and low-protein diet did not alter the amount of food intake as seen in previous studies [25, 33]. However, dams submitted to a low-protein diet showed a reduction in body weight in the last week of gestation and the first days post-delivery. Maternal protein restriction is associated with lower stores of maternal nutrients, and it has been found previously that an undernutrition-induced reduction of maternal gain of body weight is positively correlated with a low birth weight, an impaired offspring growth rate, and a loss of lean mass during development [34].

During pregnancy, there is an increase in basal hepatic glucose production, a progressive decrease in insulin sensitivity, and an associated 3.0–3.5-fold increase in insulin response in the last third of gestation [2]. Environmental stimulus as undernutrition can impair the normal hormonal/metabolic response during gestation. Herein we showed that maternal low-protein diet induced a reduction in the secretion of insulin. Our results are in accordance with previous studies where maternal low-protein (6% casein) diet induced impairment in the metabolism of glucose and secretion of insulin [1, 35, 36]. It has been suggested that the poor secretory response to glucose observed in islets from low-protein diet rats may be related to a defect in the ability of glucose to increase \(\text{Ca}^{2+}\) uptake and/or to reduce \(\text{Ca}^{2+}\) efflux from \(\beta\)-cells [36] and a reduced islet mass and/or insulin biosynthesis [3].

Given that previous studies have described an inverse relationship between maternal insulin and maternal insulin...
sensitivity with fetal growth restriction, it is expected that the processes governing fetal growth will be also affected. Indeed, we and previous investigators have showed that pups from mothers submitted to a low-protein diet present a reduction in body weight at postnatal period [24, 37–39]. These changes may result from a reduction in nutrient delivery to the fetus, then it would result in lower fetal insulin concentrations and a decrease in fetal IGF-I and IGF-II that would downregulate fetus-placental growth [40].

Little is known about the effects of maternal physical activity on the secretion of insulin. Here, we demonstrated for the first time that a controlled protocol of physical training before and during gestation increased pancreatic islets glucose-stimulated insulin secretion. This effect was particularly important once maternal protein-restriction has been shown to impair secretion of insulin leading to gestational diabetes as seen in previous study [1]. The underlying mechanism to the effects of maternal physical training on glucose-stimulated insulin secretion remains unknown but can be associated to increased pancreatic β-cell mass by upregulation of growth and survival pathways (AKT, ERK pathways) in pancreatic islets [41]. In addition, it can be resulted from the high peripheral glucose uptake by skeletal muscle in response to moderate physical training. Indeed, our previous study demonstrated that dams submitted to a low-protein diet (8% casein) during gestation present a higher fasting glycaemia than control (17% casein) while trained mothers remained with normal glycaemia [25].

Figure 1: Body weight (a) and food intake (b) during pregestation and gestation by control (C, n = 5), trained (T, n = 5), low-protein diet (LP, n = 5), and trained + low protein dams (T + LP, n = 5). The protocol of physical training was initiated four weeks before pregnancy (5 days per week, and 60 minutes per day). During gestation, duration and intensity of each session of physical exercise were progressively reduced and each group received either 17% casein diet (C and T) or 8% casein (low-protein group, LP and LP + T) isocaloric diet ad libitum. The values are presented as means ± S.E.M. *P < 0.05 versus C group using two-way ANOVA and Bonferroni’s post-hoc test.
Table 2: Indicators of litter size, litter weight, and body weight at birth to 3rd d of life.

| Groups                        | Control          | Trained          | Low protein diet | Trained + low protein diet |
|-------------------------------|------------------|------------------|------------------|---------------------------|
|                               | Mean             | S.E.M            | Mean             | S.E.M                     | Mean             | S.E.M            |
| Litter size                   | 11.0             | 0.3              | 10               | 0.2                       | 10               | 0.3              |
| Litter weight (g)             | 66.9             | 0.9              | 65.2             | 0.9                       | 55.7*            | 1.1              |
| Birth weight (g)              | 7.1              | 0.09             | 6.9              | 0.1                       | 5.7*             | 0.1              |
| Body weight (g)               |                  |                  |                  |                           |                  |                  |
| 1st d                         | 7.9              | 0.1              | 7.1              | 0.08                      | 5.9*             | 0.1              |
| 2nd d                         | 8.9              | 0.2              | 8.7              | 0.2                       | 5.9*             | 0.03             |
| 3rd d                         | 9.4              | 0.1              | 9.7              | 0.1                       | 6.1*             | 0.1              |

During gestation, the dams were submitted to physical training (5 days per week, with a progressively reduction of duration and intensity) and fed a low-protein diet. The pups into each litter were evaluated at birth to 3rd d of life. The values are presented as mean and S.E.M.

*P < 0.05 versus C using two-way ANOVA and Bonferroni’s post-hoc test.

Data reinforce the impaired effects of a maternal low-protein diet on the pancreatic islets glucose-stimulated insulin secretion that is preventable by moderate physical training.

The present study demonstrated that a controlled protocol of physical training during gestation resulted in increased insulin secretion, and mothers fed a low-protein diet during gestation showed similar results. This differential effect observed in the present study refers to dams which were previously trained when were contrasted with pregnancy and low-protein diet. These observations indicate that maternal physical exercise initiated in early pregnancy induces maternal adaptations and can be considered as a therapeutic mean of countering the effects of maternal undernutrition, which may provide a useful strategy since an exercise program may improve insulin sensitivity and fasting plasma glucose concentrations of women at risk for gestational diabetes [26].

Similarly to our results, previous study demonstrated that light-to-moderate physical activity during pregnancy is associated with reduced risk of abnormal glucose tolerance and hyperglycemia during pregnancy [42]. Rats submitted to 10 degrees slope treadmill for 5 days/week at 20 m/min, starting with a 20 min run and with a progressive daily increase of 5 min, throughout gestation showed a lower rise in blood glucose after an oral glucose load (2 g/kg body weight) than untrained pregnant rats [33]. In human, previous study has found that associations between the physical activity and insulin sensitivity and β-cell response do not appear to differ in pregnant versus nonpregnant women [43]. Further experiments are necessary to understand the mechanism underlying to those effects.

5. Conclusions

The present study showed that low-protein diet during gestation affects the secretion of insulin. In contrast, pregestational and gestational moderate physical training acts as an environmental stimulus by increasing insulin secretion and attenuating the effects of perinatal undernutrition in rats, suggesting a potential strategy for compensation of insulin resistance and preventing gestational diabetes mellitus during late pregnancy.

Acknowledgments

The authors declare no conflict of interest. This research was supported by National Council for Scientific and Technological Development (CNPq), Foundation to Support...
Science and Research from Pernambuco State (FACEPE), São Paulo Research Foundation (FAPESP), Coordination for the Improvement of Higher Level Personnel (CAPES), and Dean’s Office for Research/University of São Paulo. Authors acknowledge the National Institute of Science and Technology in Obesity and Diabetes (INOD) and the Center of Lipid Research and Education (CLEAR). All authors were responsible for critical revisions to the paper and approval of the final version. The authors are indebted to José Roberto Mendonça, Érica Portioli, and Geraldine de Souza for technical assistance.

References

[1] D. F. I. Souza, L. M. Ignácio-Souza, S. R. De L. Reis et al., “A low-protein diet during pregnancy alters glucose metabolism and insulin secretion,” Cell Biochemistry and Function, vol. 30, no. 2, pp. 114–121, 2012.

[2] J. A. Parsons, T. C. Brejle, and R. L. Sorenson, “Adaptation of islets of Langerhans to pregnancy: increased islet cell proliferation and insulin secretion correlates with the onset of placental lactogen secretion,” Endocrinology, vol. 130, no. 3, pp. 1459–1466, 1992.

[3] L. M. Ignacio-Souza, S. R. Reis, V. C. Arantes et al., “Protein restriction in early life is associated with changes in insulin sensitivity and pancreatic beta-cell function during pregnancy,” British Journal of Nutrition, vol. 5, pp. 1–12, 2012.

[4] H. C. Bertram, P. M. Nissen, C. Nebel, and N. Oksbjerg, “Metabolomics reveals relationship between plasma inositol and birth weight: possible markers for fetal programming of type 2 diabetes,” Journal of Biomedicine and Biotechnology, vol. 2011, Article ID 378268, 8 pages, 2011.

[5] J. F. Clapp, “Long-term outcome after exercising throughout pregnancy: fitness and cardiovascular risk,” American Journal of Obstetrics and Gynecology, vol. 199, no. 5, pp. 489.e1–489.e6, 2008.

[6] J. F. Clapp, “Does exercise training during pregnancy affect gestational age?” Clinical Journal of Sport Medicine, vol. 19, no. 3, pp. 241–243, 2009.

[7] C. Fleten, H. Stigum, P. Magnus, and W. Nystad, “Exercise during pregnancy, maternal prepregnancy body mass index, and birth weight,” Obstetrics and Gynecology, vol. 115, no. 2, part 1, pp. 331–337, 2010.

[8] R. Artal and M. O’Toole, “Guidelines of the American College of Obstetricians and Gynecologists for exercise during pregnancy and the postpartum period,” British Journal of Sports Medicine, vol. 37, no. 1, pp. 6–12, 2003.

[9] J. F. Clapp III, “The effects of maternal exercise on fetal oxygenation and feto-placental growth,” European Journal of Obstetrics Gynecology and Reproductive Biology, vol. 110, supplement, pp. 580–585, 2003.

[10] J. F. Clapp, H. Kim, B. Burciu, S. Schmidt, K. Petry, and B. Lopez, “Continuing regular exercise during pregnancy: effect of exercise volume on feto-placental growth,” American Journal of Obstetrics and Gynecology, vol. 186, no. 1, pp. 142–147, 2002.

[11] S. A. Hopkins, J. C. Baldi, W. S. Cutfield, L. McCowan, and P. L. Hofman, “Exercise training in pregnancy reduces offspring size without changes in maternal insulin sensitivity,” The Journal of Clinical Endocrinology and Metabolism, vol. 95, no. 5, pp. 2080–2088, 2010.

[12] B. K. Pedersen and C. Brandt, “The role of exercise-induced myokinase in muscle homeostasis and the defense against chronic diseases,” Journal of Biomedicine and Biotechnology, vol. 2010, Article ID 520258, 6 pages, 2010.

[13] H. Nicastro, N. E. Zanchi, C. R. Da Luz, D. E. S. Chaves, and A. H. Lancha Jr., “An experimental model for resistance exercise in rodents,” Journal of Biomedicine and Biotechnology, vol. 2012, Article ID 457065, 7 pages, 2012.

[14] S. Sato, K. Shirato, T. Tachiyashiki, and K. Imaizumi, “Muscle plasticity and β2-adrenergic receptors: adaptive responses of β2-adrenergic receptor expression to muscle hypertrophy and atrophy,” Journal of Biomedicine and Biotechnology, vol. 2011, Article ID 729598, 10 pages, 2011.

[15] M. A. Abdulk-Ghani and R. A. De Formonzo, “Pathogenesis of insulin resistance in skeletal muscle,” Journal of Biomedicine and Biotechnology, vol. 2010, Article ID 476279, 19 pages, 2010.

[16] M. Peppa, C. Koliaki, P. Nikolopoulos, and S. A. Raptis, “Skeletal muscle insulin resistance in endocrine disease,” Journal of Biomedicine and Biotechnology, vol. 2010, Article ID 527850, 13 pages, 2010.

[17] A. M. Das, U. Steuerwald, and S. Illsinger, “Inborn errors of energy metabolism associated with myopathies,” Journal of Biomedicine and Biotechnology, vol. 2010, Article ID 340849, 19 pages, 2010.

[18] K. Sakuma and A. Yamaguchi, “The functional role of calcineurin in hypertrophy, regeneration, and disorders of skeletal muscle,” Journal of Biomedicine and Biotechnology, vol. 2010, Article ID 721219, 8 pages, 2010.

[19] S. M. Hirabara, R. Curi, and P. Macchler, “Saturated fatty acid-induced insulin resistance is associated with mitochondrial dysfunction in skeletal muscle cells,” Journal of Cellular Physiology, vol. 222, no. 1, pp. 187–194, 2010.

[20] A. R. Martins, R. T. Nachbar, R. Gorjao et al., “Mechanisms underlying skeletal muscle insulin resistance induced by fatty acids: importance of the mitochondrial function,” Lipids in Health and Disease, vol. 11, article 30, 2012.

[21] M. F. Amorim, J. A. Dos Santos, S. M. Hirabara et al., “Can physical exercise during gestation attenuate the effects of a maternal perinatal low-protein diet on oxygen consumption in rats?” Experimental Physiology, vol. 94, no. 8, pp. 906–913, 2009.

[22] J. F. Clapp, H. Kim, B. Burciu, and B. Lopez, “Beginning regular exercise in early pregnancy: effect on feto-placental growth,” American Journal of Obstetrics and Gynecology, vol. 183, no. 6, pp. 1484–1488, 2000.

[23] J. J. García, C. Berzosa, I. Cebrián et al., “Acute exercise increases plasma total antioxidant status and antioxidant enzyme activities in untrained men,” Journal of Biomedicine and Biotechnology, vol. 2011, Article ID 540458, 7 pages, 2011.

[24] F. Falcão-Tebas, A. Bento-Santos, M. António Fidalgo et al., “Maternal low-protein diet-induced delayed reflex ontogeny is attenuated by moderate physical training during gestation in rats,” British Journal of Nutrition, vol. 107, no. 3, pp. 372–377, 2012.

[25] M. Fidalgo, F. Falcão-Tebas, A. Bento-Santos et al., “Programmed changes in the adult rat offspring caused by maternal protein restriction during gestation and lactation are attenuated by maternal moderate-low physical training,” British Journal of Nutrition, vol. 1, pp. 1–8, 2012.

[26] N. Oostdam, M. N. M. van Poppel, E. M. W. Eekhoff, M. G. A. J. Wouters, and W. van Mechelen, “Design of FitFor2 study: the effects of an exercise program on insulin sensitivity and plasma glucose levels in pregnant women at high risk for gestational diabetes,” BMC Pregnancy and Childbirth, vol. 9, article 1, 2009.
[27] K. Bayne, “Revised guide for the care and use of laboratory animals available. American Physiological Society,” The Physiologist, vol. 39, no. 4, pp. 199–211, 1996.

[28] S. Lopes De Souza, R. Orozco-Solis, I. Grit, R. Manhães De Castro, and F. Bolanos-Jiménez, “Perinatal protein restriction reduces the inhibitory action of serotonin on food intake,” European Journal of Neuroscience, vol. 27, no. 6, pp. 1400–1408, 2008.

[29] A. C. Boschero, M. Szpak-Glasman, E. M. Carneiro et al., “Oxotremorine-m potentiation of glucose-induced insulin release from rat islets involves M3 muscarinic receptors,” American Journal of Physiology, vol. 268, no. 2, pp. E336–E342, 1995.

[30] L. A. Wolfe and T. L. Weissgerber, “Clinical physiology of exercise in pregnancy: a literature review,” Journal of Obstetrics and Gynaecology Canada, vol. 25, no. 6, pp. 473–483, 2003.

[31] K. Melzer, Y. Schutz, M. Boulvain, and B. Kayser, “Physical activity and pregnancy: cardiovascular adaptations, recommendations and pregnancy outcomes,” Sports Medicine, vol. 40, no. 6, pp. 493–507, 2010.

[32] S. M. Hirabara, L. R. Silveira, F. R. M. Abdulkader et al., “Role of fatty acids in the transition from anaerobic to aerobic metabolism in skeletal muscle during exercise,” Cell Biochemistry and Function, vol. 24, no. 6, pp. 475–481, 2006.

[33] C. Muñoz, P. López-Luna, and E. Herrera, “Treadmill training enhances glucose tolerance more in pregnant than in virgin rats,” Biology of the Neonate, vol. 75, no. 5, pp. 337–342, 1999.

[34] J. E. Mallinson, D. V. Sculley, J. Craigon, R. Plant, S. C. Langley-Evans, and J. M. Brameld, “Fetal exposure to a maternal low-protein diet during mid-gestation results in muscle-specific effects on fibre type composition in young rats,” British Journal of Nutrition, vol. 98, no. 2, pp. 292–299, 2007.

[35] E. C. Vieira, E. M. Carneiro, M. Q. Latorraca et al., “Low protein diet confers resistance to the inhibitory effects of interleukin 1β on insulin secretion in pancreatic islets,” Journal of Nutritional Biochemistry, vol. 12, no. 5, pp. 285–291, 2001.

[36] E. M. Carneiro, M. A. Mello, C. A. Gobatto, and A. C. Boschero, “Low protein diet impairs glucose-induced insulin secretion from and 45Ca uptake by pancreatic rat islets,” Journal of Nutritional Biochemistry, vol. 6, no. 6, pp. 314–318, 1995.

[37] C. G. Leandro, W. da Silva Ribeiro, J. A. Dos Santos et al., “Moderate physical training attenuates muscle-specific effects on fibre type composition in adult rats submitted to a perinatal maternal low-protein diet,” European Journal of Nutrition. In press.

[38] S. E. Ozanne and C. N. Hales, “Early programming of glucose-insulin metabolism,” Trends in Endocrinology and Metabolism, vol. 13, no. 9, pp. 368–373, 2002.

[39] R. Orozco-Solis, R. J. B. Matos, S. Lopes De Souza et al., “Perinatal nutrient restriction induces long-lasting alterations in the circadian expression pattern of genes regulating food intake and energy metabolism,” International Journal of Obesity, vol. 35, no. 7, pp. 990–1000, 2011.

[40] L. Powell-Braxton, P. Hollingshead, C. Warburton et al., “IGF-I is required for normal embryonic growth in mice,” Genes and Development, vol. 7, no. 12, pp. 2609–2617, 1993.

[41] R. C. Laker, L. A. Gallo, M. E. Wlodek, A. L. Siebel, G. D. Wadley, and G. K. McConell, “Short-term exercise training early in life restores deficits in pancreatic β-cell mass associated with growth restriction in adult male rats,” American Journal of Physiology, vol. 301, no. 5, pp. E931–E940, 2011.

[42] E. Oken, Y. Ning, S. L. Rifas-Shiman, J. S. Radesky, J. W. Rich-Edwards, and M. W. Gillman, “Associations of physical activity and inactivity before and during pregnancy with glucose tolerance,” Obstetrics and Gynecology, vol. 108, no. 5, pp. 1200–1207, 2006.

[43] A. Gradmark, J. Pomeroy, F. Renström et al., “Physical activity, sedentary behaviors, and estimated insulin sensitivity and secretion in pregnant and non-pregnant women,” BMC Pregnancy and Childbirth, vol. 11, article 44, 2011.