NRMSH 1(2) (2024) 99-106

New Researches of Management in Sport and Health

Journal homepage: sanad.iau.ir/journal/nrmsh

**ORIGINAL ARTICLE**

# The Effects of Eight Weeks of Submaximal Running and High-fat Diet on IL-6 Gene Expression in the Muscle Tissue of Male Rats

Shima Ebadi, Ardeshir Zafari*

*Department of Sports Sciences, Faculty of Humanities and Art, Zanjan Branch, Islamic Azad University, Zanjan, Iran*

K E Y W O R D S

Body weight;
High-fat diet;
Inter Leukin-6;
Aerobic training

A B S T R A C T

It seems that the release of IL-6 from the contracting muscles and accumulation in the blood circulation has a close relationship with the duration and intensity of physical activity. The aime of this experimental study was to determine the effects of eight weeks of submaximal running and high-fat diet on IL-6 gene expression levels in the muscle tissue of an animal model. At the end of the two-week period of keeping under controlled conditions, 40 two-month-old male rats were randomly divided into four equal groups of control, high-fat diet, submaximal running, and a combination of high-fat diet and submaximal running. The training groups participated in the aerobic running protocol on the treadmill for five days a week for eight weeks. The polymerase chain reaction method was used to determine the levels of IL-6 gene expression in muscle tissue. One-way analysis of variance was used to determine between-group differences. The effects of high-fat diet and running with submaximal intensity on IL-6 gene expression in muscle tissue are significant. The consumption of high-fat food causes adverse changes in the expression of IL-6 gene, but eight weeks of running with sub-maximal intensity moderates the adverse effects of high-fat diet and creates favorable changes in the expression of IL-6 gene and body weight.

## Introduction

Interleukin-6 (IL-6) is an adipokine that plays a role in both innate and acquired immunity. Increasing tissue and serum concentration of interleukin-6 has negative effects on metabolism. In obese people and people who use a high-fat or high-calorie diet, the expression levels of IL-6 in fat tissue are higher, so that the expression levels of IL-6 have a direct positive relationship with the levels of body mass index and fat mass, and under inflammatory conditions in chronic obesity, interleukin-6 production increases in white adipose tissue. The expression levels of interleukin-6 are the same in adipose and muscle tissues, but the levels are higher in liver tissue (Loos *et al*., 2012).

Interleukin-6 is a systemic risk signal essentially produced by any damaged tissue. An increase in plasma IL-6 has been observed after high intensity and long-term exercise. IL-6 regulates carbohydrate and lipid metabolism in skeletal muscle and increases the proliferation of satellite cells. It seems that the release of IL-6 from the contracting muscles and subsequent accumulation in the blood circulation has a close relationship with the duration of exercise. During long-term exercise, the glycogen levels of contracting skeletal muscles decrease. Therefore, it is assumed that IL-6 release from skeletal muscles occurs during long-term exercise and in response to

***Corresponding author**: Email address: ardeshir.zafari@gmail.com
Received: 20 August 2023; Received in revised form: 27 September 2023; Accepted: 15 October 2023

the energy crisis, especially the reduction in the glycogen reserves of the contracting myofibrils. With the reduction of muscle glycogen, the dependence of contracting muscles on blood glucose as an energy source increases; thus, the release of IL-6 from contracting muscles may signal the liver to increase glucose production to prevent exercise-induced hypoglycemia. Carbohydrate consumption during exercise reduces the systemic concentration of IL-6. The increase of IL-6 during high intensity training stimulates lipolysis and fat oxidation (Ebrahimi *et al*., 2015).

Ezadi (2011) stated that increased levels of IL-6 in the long term increase insulin resistance in mice, as well as suppress human fat cells and insulin-induced glucose transport and lipogenesis. On the other hand, reduction of IL-6 activity or levels improves insulin production and insulin-receptor binding in human adipocytes and is useful for ameliorating obesity-related insulin resistance at both tissue and systemic levels. Sindhu *et al*. (2015) stated that IL-6 is related to obesity in diabetics, so that as body mass index increases, IL-6 expression also increases. Dakunha (2015) stated that in the skeletal muscle of obese elderly women, increased expression of inflammatory genes such as IL-6 causes a high inflammatory state and can affect muscle strength. On the other hand, sarcopenia, as the process of muscle loss through increasing fat, increases the fat mass which is associated with the production and release of pro-inflammatory indicators such as IL-6 and other cytokines from fat tissue, which is an important health issue. The levels of fatigue and physical activity in women treated with IL-6 were studied and it was found that fatigue is a common reaction to a systemic challenge due to the response through the action of the pro-inflammatory cytokine IL-6, which increases with a decrease in the levels of physical activity.

The anti-inflammatory effects of exercise training on the skeletal muscles of patients with chronic heart failure were also studied and the results showed that twenty minutes of cycling with seventy percent of the maximum heart rate and sixty minutes of Swedish exercise once a week for six months, did not change blood levels of IL-1β and TNFα and IL-6, but caused a significant decrease of these variables in the skeletal muscles of the patients (Dakunha *et al*., 2015). Na, Y.K. (2015) showed that in women with high body mass index, mutation or error in IL-6 gene can cause obesity. Vieira (2009) showed that performing exercise training reduces long-term inflammation in obesity caused by a high-fat diet. The effects of aerobic exercise training on the activity of cytokines were studied in twenty-eight elderly coronary artery patients. 45 minutes of aerobic training with 70-80% of maximum heart rate were performed 3 days a week for 12 weeks. Performing aerobic exercise caused a significant decrease in interleukin-1 beta, tumor necrosis factor alpha, IL-6 and C-reactive protein; meanwhile, a significant increase was observed in interleukin-10, which is a factor that inhibits the production of cytokines (Tanaka *et al*., 2014). Nemeth (2004) studied the response of leukocytes and cytokines to ten minutes of unilateral wrist flexion training, showing that IL-6 increased significantly after training. Ellomi (2009) reported a significant increase in IL-6 concentration from 51 to 83 pg $ml^{-1}$ during sixty minutes of cycling at an intensity of 75 percent of maximal oxygen consumption in trained men. The concentration of IL-6 was consistently decreased after exercise; however, it was still higher than the baseline values (six times) by six hours and reached the initial levels after two days.

Performing exercise and physical activities has been introduced as one of the important ways to deal with obesity and reduce body fat. As a result of adapting to endurance training, changes in the energy system enable the body to be more efficient in energy production; still, using different types of fuel (such as fat) causes more efficiency in energy production. The energy stored in the form of fat is used more during endurance training than other modes of training, which causes significant changes in body composition. This increase in substrates available for use increases the duration of endurance activity. Depending on the intensity of endurance training, training substrates can change. Endurance trained individuals consume fat as fuel at a higher intensity and for a longer period of time than non-trained individual, and hence they increase the lactate threshold. As a result of endurance training, the key enzymes involved in the Krebs cycle and the electron transport system increase, which have a significant contribution in increasing the capacity of muscle tissues for fat oxidation compared to carbohydrate oxidation.

Long-term exercise training increases the concentration of hormones and the sensitivity of tissues to hormones by increasing the amount of hormone receptors in the target tissue; as a result, individuals have the ability to use more available fatty acids, all of which lead to increased efficiency and better oxidation of fat sources for energy production.

In addition, athletes have an increase in the prevention and reduction of obesity by increasing the rate of resting metabolism compared to sedentary people. Daily energy expenditure and fat oxidation are improved by exercise training. The increase in resting metabolism after training may be related to an increase in fat-free mass and an increase in resting sympathetic nervous system activity and post-exercise oxygen consumption, which plays an important role in further reducing body fat mass. The exercise training protocol may increase energy expenditure and thus improve body composition and reduce fat tissue (Church *et al*., 2011; Eftekhari *et al*., 2016).

Considering the favorable effect of aerobic training on the expression of adipokines in preventing inflammation, the effect of high-fat diets on the increase of adipokines, the lack of a study to evaluate the effect of these two variables on IL-6 gene expression at the same time, as well as he contradictory results that have been obtained in the research of different human and animal groups, the need to conduct research in this regard becomes clear and well undestood. Therefore, the current research seeks to find answer to the question whether submaximal running and high-fat diet have an effect on IL-6 gene expression levels in the muscle tissue of male Wistar rats.

**Materials and Method**

The present experimental research aimed to determine the effects of eight weeks of submaximal running and high-fat diet on IL-6 gene expression levels in the muscle tissue of an animal model in a research design with four groups and a control group. At the end of the two-week period of keeping under controlled conditions, the animals were introduced and adapted to the living environment (temperature (22 ± 2°C), humidity (50 ± 5 percent) and a twelve-hour light-dark cycle), feeding conditions (*ad lib.* access to water and standard food from Pars animal feed products *viz.* ten grams of pellets for every hundred grams of body weight) and training protocol (familiarity with how to work on a five-channel smart animal electric treadmill with 0.1 millivolt fixed electric shock, 0% incline, 10-15 m $min^{-1}$. speed and 5-10 m $day^{-1}$ training duration).

After weight matching, 40 two-month-old male Wistar rats were randomly divided into four equal groups of control, high-fat diet, submaximal running, and a combination of high-fat diet and submaximal running . The independent variables of the present study included running for eight weeks with submaximal intensity and using high-fat diet for eight weeks, and the dependent variables included body weight and IL-6 gene expression in muscle tissue. All groups receiving high-fat food, in addition to their normal food, were gavaged daily by high-fat food emulsion containing the compounds in Table 1 in the amount of 1.5 mg per kilogram of body weight for eight weeks.

**Table 1.** Composition of high-fat diet used in the study.

| Ingredients | Corn oil | Sucrose | Whole milk powder | Cholestrol | Multivitamin | Tween 80 | Propylene glycol | Salt | Distilled water (ml) |
|---|---|---|---|---|---|---|---|---|---|
| Amount (gr) | 400 | 150 | 80 | 100 | 2.5 | 36.5 | 31 | 10 | 300 |

The training group participated in the aerobic training protocol on the treadmill for five days a week (Sunday, Monday, Tuesday, Thursday and Friday) for eight weeks. The training protocol was designed based on the studies of Sokhnordastjardi *et al*. (2020) and Noura *et al*. (2020). In this vein, the strain, sex, age and approximate weight of the subjects of the study were also matched based on the mentioned studis (Table 2).

The incline of the treadmill was 15% throughout the training period, and the speed of the treadmill started from twenty m $min^{-1}$. in the first week and reached thirty m $min^{-1}$. in the eighth week. The duration of training started from ten min $day^{-1}$ in the first week and reached fifty min $day^{-1}$ in the eighth week. At the beginning of the training session, each of the subjects ran for five minutes at a speed of 10-15 m $min^{-1}$ at a zero decline to warm up. Then, to reach the desired training, the speed and incline of the treadmill were increased in 5-10 minutes stepwise.

At the end of the training program, the decline of the device was back to zero degrees and the speed slowly reached 10-15 m $min^{-1}$ to cool down the subjects. The cooling time was about 5 minutes in the starting weeks and about ten minutes in the ending weeks.

**Table 2.** Eight-week protocol of running with submaximal intensity in the study.

| Running protocol with submaximal intensity | Weeks of Training | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| **Duration (M $D^{-1}$)** | 10 | 20 | 20 | 30 | 30 | 40 | 40 | 50 |
| **Treadmill speed (M $M^{-1}$)** | 20 | 20 | 24 | 24 | 26 | 26 | 30 | 30 |
| **Treadmill incline (percent)** | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |

48 hours after the last training session and after twelve hours of fasting, samples were anesthetized by intraperitoneal injection of ketamine (90 mg $kg^{-1}$) and xylazine (10 mg $kg^{-1}$), and were then killed and operated by a trained expert in a desiccator based on a predetermined schedule using the appropriate method in the shortest possible time and with minimal pain and discomfort. The muscle tissue was removed and placed in 1.5 microliter microtubes containing RNA Later at -70° C. The polymerase chain reaction method was used to determine the levels of IL-6 gene expression. The primers were received in the form of lyophilized vials and were then diluted with Sina Gene Company buffer according to the ratio indicated on the vial. After that, 180 microliters of buffer, 10 microliters of forward primer (F) and 10 microliters of reverse primer (R) were poured into the designated tubes. The sequence, length and type of primer designed for IL-6 gene were as follows.

-5-CCACCCACAACAGACCAGTA-3- (F)20bp
-5-AATTGCCATTGCACAACTCTTT-3- (R)22bp

Polymerase chain reaction was performed using the Real Q Plus 2X Master Mix Green kit from Viragen Co. After recording the obtained threshold cycles, the ratio of the target and reference gene expression was compared using the $^{\Delta\Delta Ct}$ and $2^{-\Delta\Delta C}$ formulas.

The normality of the distribution of the variables was examined with the Shapiro-Wilk test and the homogeneity of the variance of the variables was evaluated with the Levene test. One-way analysis of variance test was used to determine between-group differences by comparing the mean scores of the research variables among the groups (except the control group); also, Bonferroni's *post hoc* was used determine the place of differences between the groups. One-sample t-test was used to determine intra-group differences by comparing the mean scores of the research variables in each group with the control group. The level of significance in all tests was set at ≤ 0.05.

## Results

In Table 3, the descriptive statistics of the research variables are presented by different groups. The results of the Shapiro-Wilk and Levene's statistical tests showed that the research variables had both conditions of normality of distribution and equality of variances. The results of one-way analysis of variance showed that the difference in the body weight variable in the pre-test was not significant among different research groups [$P = 0.87$, $F_{(3, 36)} = 0.234$], while the difference in the body weight variable in the post-test was significant [$P \leq 0.001$, $F_{(3,36)} = 250.30$]. This difference was significant among all groups ($P \leq 0.001$) as well. The results of paired samples t-test also showed that changes in body weight within the control groups [$P \leq 0.001$, $t_{(9)}= 25.53$], high-fat diet [$P \leq 0.001$, $t_{(9)}= 30.69$], running [$P \leq 0.001$, $t_{(9)} = 12.61$] and high-fat diet and running [$P \leq 0.001$ , $t_{(9)}= 18.92$] were significant, which showed an increase in body weight by 26.10% in the control group, 46.36% in the high-fat diet group, 15.64% in the running group, and 25.71% in the high-fat diet and running group. The normal increase in body weight due to age in the control group indicates that the high-fat diet caused more weight gain in eight weeks; on the other hand, in the sub-maximal intensity running group, the estimated weight gain was less than the control group and the high-fat diet and running group, and this significant difference was probably due to the effects of sub-maximal intensity running. The levels of weight gain in the control group and the high-fat diet with running group were almost the same, which shows that sub-maximal running was able to control the very high weight gain caused by high-fat food consumption, and maintain it at the level of control group and similar to the normal process of weight gain. Finally, running at a submaximal intensity resulted in more favorable effects and prevented excessive weight gain caused by high-fat diet.

**Table 3.** Descriptive statistics of the research variables in different study groups.

| Group | Body weight (gr) Pretest | | Body weight (gr) Posttest | | IL-6 | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| **Control** | 184.10 | 5.02 | 232.10 | 5.19 | 1.00 | Reference |
| **High-fat diet** | 183.80 | 4.63 | 269.00 | 5.29 | 2.295 | 0.050 |
| **Running with submaximal intensity** | 183.50 | 5.37 | 212.50 | 4.08 | 0.848 | 0.055 |
| **High-fat diet with running** | 182.40 | 4.90 | 229.30 | 4.37 | 1.876 | 0.048 |

The results of one-way analysis of variance (Table 4) showed that the difference in mean scores of IL-6 in the muscle tissue of male Wistar rats after eight weeks of running with sub-maximal intensity and using high-fat diet was significant [$P \leq 0.001$, $F_{(2,27)} = 2083.18$]. The results of Bonferroni's *post hoc* test showed that the difference between the high-fat diet and high-fat diet and running groups was significant ($P \leq 0.001$), which indicates the interactive effect of running with sub-maximal intensity and high-fat diet on changes of the variable IL-6 in muscle tissue. The difference between the high-fat diet and submaximal running groups was significant ($P \leq 0.001$), which indicates the effect of submaximal running on IL-6 changes in muscle tissue. The difference between the high-fat diet and running with the submaximal running groups ($P \leq 0.001$) was also significant, indicating the effect of submaximal running on IL-6 changes in muscle tissue. On the other hand, the comparison of different groups with the control group also shows the effect of high-fat diet, running with sub-maximal intensity and their interaction on changes in the variable IL-6 in muscle tissue. Between-group differences in the means of the variable IL-6 in the muscle tissue of high-fat diet and control ($P \leq 0.001$), high-fat diet with running and control ($P \leq 0.001$) and submaximal running and control $P \leq 0.001$) were significant; therefore, it seems that the effects of high-fat diet, the combination of high-fat diet and running, as well as running with sub-maximal intensity on IL-6 of muscle tissue are significant (Table 5).

**Table 4.** Differences in the means of the variable IL-6 in the muscle tissue of rats.

| Variable | Source of variations | Sum of squares | df | Mean of squares | F value | P |
|---|---|---|---|---|---|---|
| **IL-6** | Between-group | 11.087 | 2 | 5.544 | 2083.186 | ≤ 0.001 |
| | Within-group | 0.072 | 27 | 0.003 | | |
| | Total | 11.159 | 29 | ///// | | |

**Table 5.** The results of one-sample *t*-test to compare IL-6 levels in the muscle tissue of the study groups with the levels in the control group.

| Group | Mean | SD | Difference of means | *t* value | df | P |
|---|---|---|---|---|---|---|
| **High-fat diet** | 2.295 | 0.050 | 1.295 | 80.57 | 9 | ≤ 0.001 |
| **High-fat diet with running** | 1.876 | 0.048 | 0.786 | 57.02 | 9 | ≤ 0.001 |
| **Running with submaximal intensity** | 0.848 | 0.055 | -0.152 | 8.71 | 9 | ≤ 0.001 |

## Discussion

Obesity is a heterogeneous condition that occurs as a result of increased energy intake due to the consumption of high-calorie and high-fat foods and a decrease in energy expenditure due to a decrease in physical activity, and the response of people to the standard therapeutic programs is variable. Among the methods of weight loss based on therapeutic and medical interventions, we can mention the use of anti-obesity drugs and appetite suppressant drugs. These drugs, which have limited to moderate weight loss effects, have side effects, and usually, weight return can be expected after stopping the drug. Surgery, which is feasible for few people, has better, and more lasting effects, but the risks of surgery and its side effects should not be forgotten. Limiting the intake of calories and following a strict low-calorie diet is another way to deal with obesity, which can cause rapid and high weight loss. This method also has adverse side effects and there is a possibility of weight gain. Performing physical activities and exercises under the supervision of experts in sports science and exercise physiology is also a safe, low-risk way and has low to moderate effects in dealing with obesity. In this method, weight loss is gradual and long-term, and it is possible to regain weight after stopping exercise. In addition, this method has favorable and beneficial effects in strengthening the heart and respiratory systems, blood vessels and muscles, as well as regulating hormones.

Exercise plays an essential role in human health in two ways. First, long-term participation in physical activity prevents many chronic diseases caused by today's modern society that disturb the normal functioning of the body. Second, exercise helps to rehabilitate these diseases. Therefore, exercise can be a very important factor in the prevention of these diseases, and in some cases, exercise can eliminate or reduce the signs and symptoms of these diseases (Ossanloo *et al*., 2012). Muscle glycogen breakdown and calcium are two important factors that regulate IL-6 gene transcription and cytokine production in skeletal muscle during exercise. Immune cells are stimulated and activated during exercise in response to muscle damage and also through the application of stress hormones that are released in response to the increased metabolic needs of the body's core temperature during exercise. Interference between immune cells and stress hormones contribute to fluctuations in cytokine production. An increase in core temperature during exercise can reduce the absorption of endotoxins (lipopolysaccharide) through the wall of the small intestine into the bloodstream, and this can alter cytokine production. Oxidative stress caused by exercise is another factor that affects the production of cytokines. Oxidative stresses are the result of oxidative reactions in skeletal muscles and especially muscle damage. During exercise, endogenous antioxidant enzymes and dietary antioxidant supplements can potentially reduce cytokine production directly by neutralizing free radicals or inhibit the activity of redox-sensitive signal transduction pathways. The produced IL-6 can act locally within the muscle itself in a paracrine manner or be secreted into the blood and be able to cause systemic effects. In the liver, blood IL-6 increases the output of glucose from the liver and the production of C-reactive protein. In adipose tissue, this cytokine is produced locally, which together with blood IL-6 can increase lipolysis. Blood IL-6 can stimulate cortisol by activating the hypothalamus-pituitary-adrenal axis and this increases lipolysis (Ebrahimi *et al*., 2015). Therefore, it seems that the effects of high-fat diet and running with submaximal intensity on IL-6 variable in muscle tissue are significant, so that the consumption of high-fat food causes adverse changes in the expression of this inflammatory gene, but eight weeks of running with sub-maximal intensity moderates the adverse effects of high-fat diet and creates favorable changes in the expression of this inflammatory gene and body weight.

**Acknowledgements**

This research is the results of a MsC. thesis. The authors thank and appreciate all the people who participated in this research.

**Conflict of interests**

The authors have no conflict of interest.

**References**

Church TS, Thomas DM, Tudor-Locke C, Katzmarzyk PT, Earnes, CP, Rodarte RQ, (2011) Trends over 5 decades in US occupation-related physical activity and their association with obesity. PloS one. 6(5), e19657.

Da Cunha Nascimento D, de Sousa NMF, de Sousa Neto IV, Tibana RA, de Souza VC, Vieira DCL (2015) Classification of pro-inflammatory status for interleukin-6 affects relative muscle strength in obese elderly women. Aging Clinical and Experimental Research. 27(6), 791-797.

Ebrahimi M, Khenar Sanami S (2015) Effects of high fat diet and high intensity aerobic training on interleukin 6 plasma levels in rats. Modares Journal of Medical Sciences: Pathobiology. 18(3), 110-116.

Eftekhari E, Zafari A, Gholami M (2016) Physical activity, lipid profiles and leptin. The Journal of Sports Medicine and Physical Fitness. 56(4), 465-469.

Ellomi M, Ben Ounis O, Makni E, Van Praagh E, Tabka Z, Lac G (2009) Effect of individualized weight-loss programmes on adiponectin, leptin and resistin levels in obese adolescent boys. Acta Pediatr. 98(9), 1487-1493.

Ezadi M, Sohaily S, Parsian H, Zand A (2011) Pro-inflammatory cytokine Interleukin-1 beta is associated with cardiovascular fitness in sedentary diabetic patients. Journal of Biodiversity and Environmental Sciences (JBES). 1(2), 37-44.

Loos RJ (2012) Genetic determinant of common obesity and their value in prediction. Best Practice & Research Clinical Endocrinology & Metabolism. 26(2), 211-226.

Na YK, Hong HS, Lee WK, Kim DS (2015) Increased methylation of interleukin 6 gene is associated with obesity in Korean women. Molecular and Cells. 38(5), 452-456.

Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pederson BK (2004) IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. The Journal of Clinical Investigation. 113(9), 1271-1276.

Noura M, Arshadi S, Zafari A, Banaeifar A (2020) The effect of running on positive and negative slopes on TNF-α and INF- γ gene expression in the muscle tissue of rats with Alzheimer's disease. Journal of Basic Research in Medical Science. 7(1), 35-42.

Ossanloo P, Najar L, Zafari A (2012) The Effects of Combined Training (Aerobic Dance, Step Exercise and Resistance Training) on Body Fat Percent and Lipid Profiles in Sedentary Females of AL_ZAHRA University. European Journal of Experimental Biology. 2(5), 1598-1602.

Ouchi N, Parker JL, Lugus JJ, Walsh K (2011) Adipokines in inflammation and metabolic disease. Nature Reviews Immunology. 11(2), 85-97.

Sindhu S, Thomas R, Shihab P, Sriraman D, Behbahani K, Ahmad R (2015) Obesity is a positive modulator of IL-6R and IL-6 expression in the subcutaneous adipose tissue: significance for metabolic inflammation. PloS one. 10(7), e0133494.

Sokhanvardastjerdi S, Banaeifar A, Arshadi S, Zafari A (2020) the Effect of 12 Weeks Aerobic Training on PDX-1 and GLUT2 Gene Expression in the Pancreatic Tissue of Type 2 Diabetic Rats. Iranian journal of Diabetes and Obesity. 12(2), 98-103.

Tanaka T, Narazaki M, Kishimoto T (2014) IL-6 in inflammation, immunity, and disease. Cold Spring Harbor Perspective in Biology. 6(10), a016295.

Vieira VJ, Valentine RJ, Wilund KR, Antao N, Baynard T, Woods JA (2009) Effects of exercise and low-fat diet on adipose tissue inflammation and metabolic complications in obese mice. American Journal of Physiology – Endocrinology and Metabolism. 296(5), 1164-71.