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# RESPONSES OF IL-6 AND INSULIN RESISTANCE TO ACUTE CIRCUIT RESISTANCE EXERCISE

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## ABSTRACT

Systemic concentration of IL-6 is an important factor that used in detection of cardio-vascular and metabolic disease and Physical activity can changes its plasma levels. The purpose of this study was to investigate the effects of acute circuit resistance exercise on IL-6 and Insulin Resistance (IR).

Fourteen subjects (with Mean ± SD; age, 25 ± 2.1 years; height, 178 ± 4.6 cm; BMI, 23.7 ± 2.7 kg/m$^2$; fat% 15.3 ± 4.918) had been examined. After familiarization sessions and determining of maximal strength (1-RM), all subjects completed circuit resistance exercise trials at an intensity corresponding to 55% of 1-RM. The resistance exercise protocols consist of 3 sets of 15 repetitions and 2min rest between circuits. With one week interval all subject participated in control session. Four blood samples were obtained before exercise, immediately after exercise, 1h recovery and next day morning in exercise session and same time in control session, and analyzed for IL-6, insulin and glucose. IR calculating using glucose and insulin concentration. To determine the effect of resistance exercise on factors changes repeated measure ANOVA 2*4 had been used.

Repeated measure ANOVA analysis showed significant main effects of exercise on IL-6 and IR. During 1h recovery IL-6, insulin and glucose values returning to baseline levels and insulin and glucose concentration remained unchanged in 24h post exercise (P>0.05).

The elevation in IL-6 immediately after acute resistance circuit exercise is seems to stimulate using fat disposal and liver glycogen after exercise and probably recovery periods, and possibly circuit resistance exercise causes the activation of mechanism that responsible for reducing body inflammatory responses.

**Keywords: Interleukin, Circuit Resistance Exercise, Inflammatory Markers**

## INTRODUCTION

Chronic systemic inflammation is an important risk factor for several major clinical diseases, such as cardiovascular disease (CVD) and diabetes. Inflammation is the responses of immune system to infection or tissue damages that trigger production of cytokine locally **[1]**. Local inflammation responses along with systemic responses that known as Acute Phase Response (APR) occur simultaneously and during this processes circulating levels of inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are elevated **[2,3].** Elevations in CRP levels are stimulated by IL-6 production **[4,5].** IL-6 is biologically active substance that not only produced by immune cells but also produced by fat tissue and contracting skeletal muscle during exercise without inflammation **[1,6]** and has been shown to stimulate anti-inflammatory cytokines such as IL-1 receptor antagonist and IL-10 and inhibit the production of pro-inflammatory TNF-a **[7].** Both CRP and IL-6 have been shown to play independent roles in the development of atherothrombosis and thus may represent a mechanistic link between obesity and the development of coronary heart disease and overall CVD **[8].** IL-6 production and secretion can be involved in the regulation of glucose homeostasis and insulin sensitivity of tissues and increase tissues insulin resistance to overcome abnormal metabolic systems functions **[9].**

Following exercise, the basal plasma IL-6 concentration may increase up to 100 fold, but less dramatic increases are more frequent **[10].** Importantly, the contracting skeletal muscle *per se* appears to be one of the main sources of the IL-6 in the circulation in response to exercise: In resting human skeletal muscle, the IL-6 mRNA content is very low, while small amounts of IL-6 protein predominantly in type I fibers may be detected using sensitive immunohistochemical methods **[11].**

Acute exercise may be an impetus for the inhibition of chronic disease development via the inducement of post exercise inflammatory responses **[12].** Accordingly, it has been

demonstrated that plasma IL-6 concentration increases during differing bouts of acute exercise **[13,14,15].** Pedersen and Febbraio (2008) report IL-6 as having anti-inflammatory capacities and as the earliest and most marked post-exercise inflammatory respondent; stimulating the appearance of anti-inflammatory cytokines including IL-10, IL-1ra, and soluble tumor necrosis factor receptors, whilst also occurring in a tumor necrosis factor-alpha independent manner **[12].** Such anti-inflammatory contributions during acute exercise have shown to be associated with enhanced metabolic function in both non-insulin dependent diabetes mellitus (NIDDM) and normo-glycaemic subjects **[13].** However, to date few studies report the acute resistance exercise-induced IL-6 and IR responses.

Therefore, the aim of this study is to investigate the acute exercise-induced plasma IL-6, and IR to circuit resistance exercise, within a young aged, recreationally active and disease-free subject population. Based on previous research, it was hypothesized that acute resistance exercise protocol would cause higher post exercise circulating concentrations of all hormones that involved in substrate utilization. It was also hypothesized that strenuous exercise would elevate metabolite levels of glucose and insulin as well as IL-6 concentrations. Studies about the effects of acute circuit resistance exercise on plasma IL-6 and insulin resistance are controversial, thus, we were interested to investigate effects of acute circuit resistance exercise that alters both aerobic and anaerobic systems on IL-6 and IR immediately after acute exercise, 1h and 24h recovery periods.

## SUBJECTS AND METHODS

### *Subjects*

Fourteen healthy men (Mean ± SD; age, 25 ± 2.1 years; height, 178 ± 4.6 cm; BMI, 23.7 ± 2.7 kg/m$^2$; fat% 15.3 ± 4.918) with recreational physical activity participated voluntary in this study. Participants were free of drug and medication and had no history of endocrine disorders or diabetes and obesity before and during this study. The Islamic Azad University, Tehran Branch, Ethics Committee initially approved the experimental procedures and study protocols, which were fully explained to all subjects, and a written consent form was signed after having read and understood the details of the experiments. To control for the possible effect of diet and physical activity, all exercise session took place after an overnight fast and subjects were asked to have minimal activity 48h before beginning exercise test.

### Anthropometric measurements and 1-Reapeted Maximum (1-RM)

Although all subjects have some experiment about working with weights, one familiarization session was designed to habituate subjects with different resistance exercises using weight-training machines, testing procedures and laboratory environment. As well as in this session height was measured to the nearest 0.5 cm without shoes using a calibrated scale (Cranlea and Company, Bourneville, Birmingham, UK) and Body mass and total body fatness were measured using the X-scan plus II Segmental Body Composition Analyzer (X-scan plus II, Korea) with correction for light indoor clothing. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared ($BMI=weight_{(kg)}/height_{(m)}^2$). Following familiarization session, subjects were asked to report to the laboratory for an additional session designed to determine 1RM for seven exercises including upper and lower body parts. To minimize the possibility of injury, short bouts of general and specific warm-up were performed before determination of the 1-RM. The general warm up consisted 5 min of riding a stationary bicycle, while the specific warm-up encompassed two sets (eight repetitions) of progressive resistance exercises similar to the actual exercises utilized in the main experiment. After the warm-up, subjects performed the 1RM test using the Brzycki method **[16]**, the heaviest weight successfully lifted using the correct technique for each exercise was considered as the 1RM and used to calculate 55% resistances for each exercise.

**Experimental design**

After the maximal exercise test and determination of 1-RM, subjects were asked to report to the physiology laboratory on two additional, but separate occasions starting at 08:00 AM. The two sessions were separated by at least 5 days. Exercise sessions included the performance of 3 sets of 15 repetitions at 55% of 1-RM and its duration was 18-22 minutes. The exercise session was preceded by general and specific warm-ups and two minute rest was given between exercises and sets. The exercises and order of performance were as follow: latissimus pull down, leg extension, triceps pushdown, leg curl, bench press, and back squat. The exercise was followed by 1h of recovery, with the subjects remaining seated throughout. In control session all subjects rest in sitting position. To control for the possible effect of diet and physical activity, all trials took place after an overnight fast and also all subjects were asked to not have strenuous physical activity 48h before beginning of the test. Care was taken to ensure that the environmental conditions (ambient

temperature, 20-21 ℃ and relative humidity, 52-58%) were identical during all exercise sessions.

**Blood sampling and analysis**

Blood samples were obtained from antecubital vein before exercise, immediately after the exercise, after 1-h recovery and 24-h following the exercise. Plasma was separated by centrifugation (1600g, 15min at 4°C) immediately after blood sampling and divided into three aliquots. The aliquots were frozen and stored at -70°C for subsequent analyses (within 3-4 weeks). The samples were analyzed for IL-6, insulin and glucose. Plasma IL-6 was measured using a commercial human IL-6, ELISA (CUSABIO BIOTECH, Wuhan, China) and the interassay CV and sensitivity were 5.3% and 7.81 pg/mL, respectively. Plasma insulin was determined by human ELISA kit (Mercodia, Uppsala, Sweden) and the interassay CV and sensitivity were 4.1% and 0.07 lg/L, respectively. Plasma glucose was determined by an enzymatic, colorimetric method (glucose: GOD-PAP, glucose oxidase-aminoantipyrine, Pars Azmoun, Tehran, Iran). Before, immediately after intervention, 1h recovery and next day after acute exercise insulin resistance in fasting state was determined using a homeostasis model assessment (HOMA-IR) and was calculated from fasting insulin (lU/ml) and fasting glucose (mmol/l) as follows: HOMAIR=(insulin*glucose)/22.5 **[16].**

**Statistical analysis**

Descriptive statistics were computed and distributions of all variables were assessed for normality. A two-way ANOVA with repeated measures across session **x** 2 (exercise and rest) and time **x** 4 (rest, exercise, recovery and next day) was employed to examine differences in mean values. When ANOVA indicated the presence of a significant time difference, Bonferoni's post-hoc test was used to determine differences between times. Baseline values were compared statistically using paired -tests. Data are presented as mean (±SE) unless otherwise stated. Statistical significance was set at $P<0.05$.

**RESULTS**

Physiological characteristics of the subjects are presented in Table 1. Resting levels of all factors in two sessions showed no significant differences ($P<0.05$). Results for 1RM testing included chest press (75.8 ± 3.2 kg), shoulder press (68.8 ± 4.3 kg), lat pull-down (64.9 ± 2.9 kg) for upper-body strength, and leg press (184.1 ± 5.2 kg), leg curl (42.1 ± 2.6 kg), leg extension (58.5 ±4.2 kg), static lunge (44.3 ± 3.1 kg) for lower-body strength. The acute effects of circuit resistance exercise and the control session on plasma IL-6 levels are

presented in Fig. 1. Repeated measure ANOVA analysis showed significant main effects of exercise on IL-6 ($F_{3,39}=7.21$, P=0.001). Compared with pre-intervention values, Post-hoc analyses revealed a highly significant increase at post exercise IL-6 (P=0.008). An average increase of 98% was observed at post exercise IL-6. During 1hrecovery these values increased again and reached above post-exercise levels. In control session plasma IL-6 showed no significant change ($p<0.05$). The values of 24h post exercise IL-6 remained unchanged at exercise and control sessions.

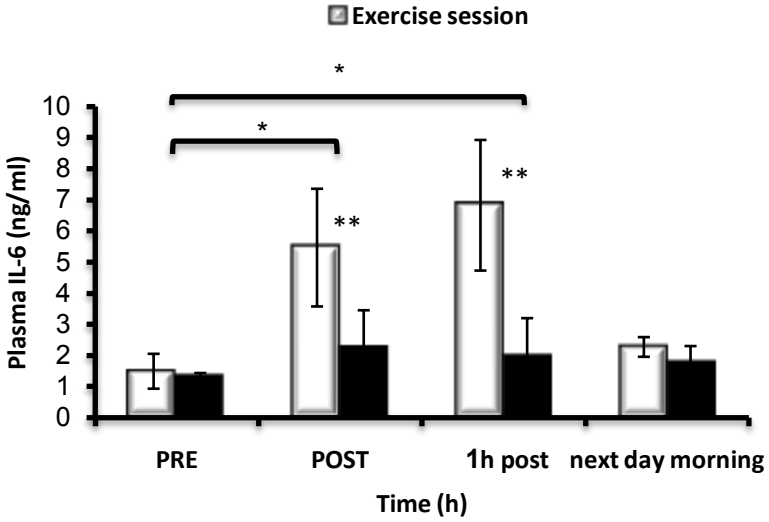


**Figure 1: Mean (±SE) values of plasma IL-6 at rest, post-exercise, after 1h and next day morning recovery for both exercise and control session. A significant main (P<0.01) effect of exercise is denoted by *. Significant (P<0.05) difference of interaction between time and session is denoted by ****

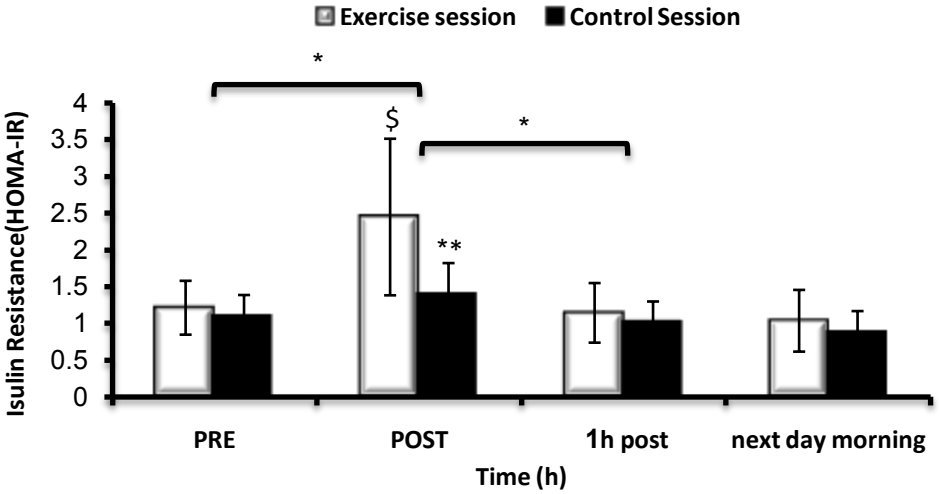


**Figure 2: Mean (±SE) values of Insulin Resistance at rest, post-exercise, after 1h and next day morning recovery for both exercise and control session. A significant main (P<0.01) effect of exercise is denoted by *. Significant (P<0.05) difference at rest is denoted by ** and $**

Statistical analysis of the data indicated a significant main effect of exercise (Table 2) for insulin and glucose concentrations ($F_{1.57,18.65}=6.53$, $F_{3,39}=3.30$, respectively; all $P<0.05$). Post-hoc analyses showed a significant difference between rest and immediately after circuit resistance exercise values for both variables ($P<0.05$). During 1h recovery insulin and glucose values returning to baseline levels and insulin and glucose concentration remained unchanged in 24h post exercise ($P>0.05$).

Data analysis of insulin resistance based on HOMA-IR (Fig 2) revealed a significant main effect of exercise ($F_{2.58,16.40}= 8.74$, $p<0.05$). Post-hoc analyses revealed a highly significant difference between rest and post exercise IR ($P=0.008$). An average increase of 109% was observed in after resistance exercise. During 1h recovery, these values declined and reached pre-exercise values and no change of 24h post exercise IR was observed.

**DISCUSSION**

The purpose of this study was to investigate the effects of resistance exercise intensity on IL-6 and IR in healthy men. Results of present study demonstrated an overall significant 98 percent increase of IL-6 after acute circuit resistance exercise that comparing with control session. Majority of studies about responses of inflammatory markers to acute exercise is limited to endurance and some classic resistance training exercise **[17,18].** Phillips et al (2010) showed a significant increase in IL-6 in response to acute exercise resistance with different intensity and repetitions, compared with the control group, also higher overall exercise volume cause higher increase in IL-6 that within 6 hours of after the activity has returned to resting level **[19].** Current literature represents IL-6 to have both pro and anti-inflammatory properties **[20,21,22]**. IL-6 as a pro-inflammatory cytokine expressed within the plasma is an indicator of chronic low grade inflammation and is a strong predictor of future development of CVD **[20,22,23].** Despite the sedentary cohort exhibiting normal resting values of IL-6 concentration of $1.41 \pm 0.33$ pg mL-1, is suggestive of moderate risk for future development of inflammatory diseases such as CVD **[24,25,26].**

Physical activity may offer protection against, and be useful in the treatment and prevention of chronic diseases associated with low-grade inflammation **[22,27].** The findings of the present study indicate the magnitude of the acute exercise-induced inflammatory response appears to be determined in part by the type of the exercise bout performed. The suggested type effect of circuit resistance exercise on the acute inflammatory response is apparent

through the higher volume of this type of exercise; however in studies of Mendham and et al (2011), when standardized for exercise duration done, it appears the modality (aerobic vs. resistance) of exercise performed was not a major determinant of the acute plasma IL-6 and CRP response to exercise **[28].**

The release of IL-6 from contracting skeletal muscle **[22,29]** and the subsequent increases in plasma IL-6 concentration during and immediately after exercise are a consistent finding in the research literature **[13,20].** Somewhat in agreement, the IL-6 changes from pre to post and 1h recovery values. Previously, Fischer (2006) reported that the magnitude of the IL-6 response is highly dependent on the duration of exercise, with duration accounting for more than 50% of plasma IL-6 variation. However, the present study indicates that when performing acute circuit resistance exercise, exercise volume is a major contributor to the ensuing IL-6 response **[15].**

IL-6 is capable of catabolic some catabolic features that include increased energy expenditure, lipolysis, fat oxidation and release of glucose by suppressing insulin signaling and cortisol elevations **[18].** Insulin and Glucose increase immediately after acute exercise has different mechanism compared with meals or oral glucose tolerance test (OGTT) because of muscle contractions and more metabolic stress that applied on body is responsible for increasing insulin secretion and IR immediately after exercise. Increased transport of glucose and fatty acids into the bloodstream from the liver and adipose tissue may improve the fuel consumption of muscle tissue and other organs, in particular **[31].** Insulin resistance significantly increased immediately after exercise compared to the control session. In most studies after endurance and resistance activities increased insulin resistance were observed **[32].** Increased insulin resistance immediately after the activity is due to increased blood flow insulin that secreted from Pancreas beta cells for decrease blood glucose. Some researchers, introduced as IL-6 stimulator of insulin secretion in pancreatic beta cells **[33,34]**, on the one hand because of the fasting conditions and the high volume of activity is likely that increase in IL-6 is stimulator of liver for release glucose and combination of these factors resulted in an immediate increase in insulin resistance immediately after the exercise.

**CONCLUSION**

In conclusion overall results showed a significant increase in IL-6 and insulin resistance after circuit resistance exercise. It

seems that acute circuit resistance exercise stimulated cytokine activity immediately following the activity and suggest that this type of exercise can affects inflammatory and anti inflammatory responses. In order to have detailed evaluate of circuit resistance exercise on inflammatory markers especially in recovery periods, comparing this type of exercise with other type of endurance and resistance training with controlling exercise volume is recommended.

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**REFERENCES**

**[1]**Petersen AM, Pedersen BK. 2005. The anti-inflammatory effect of exercise. Journal of Applied Physiology (Bethesda, Md : 1985), 98(4):1154-62.

**[2]**Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. 1999. Elevated C-reactive protein levels in overweight and obese adults. JAMA, 282(22):2131-5.

**[3]**Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. 2012. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. 1999. Biochemical and Biophysical Research Communications, 425(3):560-4.

**[4]**Aoi W, Naito Y, Takagi T, Tanimura Y, Takanami Y, Kawai Y, et al. 2013. A novel myokine, secreted protein acidic and rich in cysteine (SPARC), suppresses colon tumorigenesis via regular exercise. GUT, 62(6):882-9.

**[5]**Smith JK, Dykes R, Douglas JE, Krishnaswamy G, Berk S. 1999. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. JAMA,281(18):1722-7.

**[6]**Pedersen BK, Febbraio MA. 2012. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nature Reviews Endocrinology, 8(8):457-65.

**[7]**Steensberg A, van Hall G, Osada T, Sacchetti M, Saltin B, Klarlund Pedersen B. 2000. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. The Journal of Physiology, 529 Pt 1:237-42.

**[8]**Blake GJ, Ridker PM. 2002. Inflammatory bio-markers and cardiovascular risk prediction. Journal of Internal Medicine, 252(4):283-94.

**[9]**Kraemer WJ, Hatfield DL, Comstock BA, Fragala MS, Davitt PM, Cortis C, et al. 2014. Influence of HMB

supplementation and resistance training on cytokine responses to resistance exercise. Journal of the American College of Nutrition, 33(4):247-55.

**[10]** White LJ, Castellano V, Mc Coy SC. 2006. Cytokine responses to resistance training in people with multiple sclerosis. Journal of Sports Sciences, 24(8):911-4.

**[11]** Ploeger HE, Takken T, de Greef MH, Timmons BW. 2009. The effects of acute and chronic exercise on inflammatory markers in children and adults with a chronic inflammatory disease: a systematic review. Exercise Immunology Review, 15:6-41.

**[12]** Kramer HF, Goodyear LJ. 2007 Exercise, MAPK, and NF-kappaB signaling in skeletal muscle. Journal of Applied Physiology (Bethesda, Md : 1985), 103(1):388-95.

**[13]** Pedersen BK, Febbraio MA. 2008. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiological Reviews, 88(4):1379-406.

**[14]** Febbraio MA, Pedersen BK. 2002. Muscle-derived interleukin-6: mechanisms for activation and possible biological roles. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 16(11):1335-47.

**[15]** Fischer CP. 2006. Interleukin-6 in acute exercise and training: what is the biological relevance? Exercise Immunology Review, 12:6-33.

**[16]** Kraemer WJ, Fleck SJ. 2007. Optimizing strength training: designing nonlinear periodization workouts: Human Kinetics.

**[17]** Calle MC, Fernandez ML. 2010. Effects of resistance training on the inflammatory response. Nutrition Research and Practice, 4(4):259-69.

**[18]** Izquierdo M, Ibanez J, Calbet JA, Navarro-Amezqueta I, Gonzalez-Izal M, Idoate F, et al. 2009. Cytokine and hormone responses to resistance training. European Journal of Applied Physiology, 107(4):397-409.

**[19]** Phillips MD, Patrizi RM, Cheek DJ, Wooten JS, Barbee JJ, Mitchell JB. 2012. Resistance training reduces subclinical inflammation in obese, postmenopausal women. Medicine and Science in Sports and Exercise, 44(11):2099-110.

**[20]** Petersen AM, Pedersen BK. 2006. The role of IL-6 in mediating the anti-inflammatory effects of exercise. Journal of Physiology and

Pharmacology: An Official Journal of the Polish Physiological Society, 57 Suppl 10:43-51.

**[21]** Pedersen BK. 2006. The anti-inflammatory effect of exercise: its role in diabetes and cardiovascular disease control. Essays in Biochemistry, 42:105-17.

**[22]** Mathur N, Pedersen BK. 2008. Exercise as a mean to control low-grade systemic inflammation. Mediators of Inflammation, 2008:109502.

**[23]** Benatti FB, Pedersen BK. 2014. Exercise as an anti-inflammatory therapy for rheumatic diseases-myokine regulation. Nature Reviews Rheumatology, 193.

**[24]** Autenrieth C, Schneider A, Doring A, Meisinger C, Herder C, Koenig W, et al. 2009. Association between different domains of physical activity and markers of inflammation. Medicine and Science in Sports and Exercise, 41(9):1706-13.

**[25]** Glund S, Krook A. 2008. Role of interleukin-6 signalling in glucose and lipid metabolism. Acta Physiologica (Oxford, England), 192(1):37-48.

**[26]** Pedersen BK. 2011. Muscles and their myokines. The Journal of Experimental Biology, 214(Pt 2):337-46.

**[27]** Pedersen BK. 2011. Exercise-induced myokines and their role in chronic diseases. Brain, Behavior, and Immunity, 25(5):811-6.

**[28]** Mendham AE, Duffield R, Marino F, Coutts AJ. 2014. Differences in post-exercise inflammatory and glucose regulatory response between sedentary indigenous Australian and Caucasian men completing a single bout of cycling. American Journal of Human Biology: The Official Journal of the Human Biology Council, 26(2):208-14.

**[29]** Pedersen L, Pilegaard H, Hansen J, Brandt C, Adser H, Hidalgo J, et al. 2011. Exercise-induced liver chemokine CXCL-1 expression is linked to muscle-derived interleukin-6 expression. The Journal of Physiology, 589(Pt 6):1409-20.

**[30]** Pedersen BK, Steensberg A, Schjerling P. 2001. Muscle-derived interleukin-6: possible biological effects. The Journal of Physiology, 536(Pt 2):329-37.

**[31]** Gomez CR, Karavitis J, Palmer JL, Faunce DE, Ramirez L, Nomellini V, et al. 2010. Interleukin-6 contributes to age-related alteration of cytokine production by macrophages. Mediators of Inflammation, 2010:475139.

**[32]** Ishii T, Yamakita T, Sato T, Tanaka S, Fujii S. 1998. Resistance training improves insulin sensitivity in NIDDM subjects without altering maximal oxygen uptake. Diabetes Care, 21(8):1353-5.

**[33]** Kim ES, Im JA, Kim KC, Park JH, Suh SH, Kang ES, et al. 2007. Improved insulin sensitivity and adiponectin level after exercise training in obese Korean youth. Obesity (Silver Spring, Md), 15(12):3023-30.

**[34]** Mizgier ML, Casas M, Contreras-Ferrat A, Llanos P, Galgani JE. 2014. Potential role of skeletal muscle glucose metabolism on the regulation of insulin secretion. Obesity Reviews: an Official Journal of the International Association for the Study of Obesity, 15(7):587-97.