# The Effect of Different Endurance Exercise Intensities on the Expression of RIP140 Protein in Visceral Adipose Tissue in Diabetic Rats

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## Abstract

**Objective:** RIP140 is one of the proteins that play a role in regulating and metabolizing lipid droplets. The aim of this study was to compare the three endurance training intensities (low, moderate and high) on the expression of RIP140 protein in visceral adipose tissue and insulin resistance in male diabetic wistar rats.

**Materials and Methods:** Forty male wistar rats were assigned to five groups (n= 8) including diabetic group with low intensity endurance training (DLE), moderate intensity endurance training (DME), high intensity endurance training (DHE), diabetic control (DC) and healthy nondiabetic sedentary (NS) groups. After induction of diabetic rats by injection of streptozotocin, endurance training was performed with different intensities for eight weeks, three sessions per week. The relative expression of RIP140 protein was measured by western blot technique. To compare groups, dependent variables were analyzed by One Way ANOVA، Kruskal–Wallis and the post hoc Mann-Whitney U Test.

**Results:** Results showed significant effect of exercise on insulin resistance values (*P*-value: 0.001). Comparison of expression of RIP140 protein in diabetic and high intensity endurance training group, diabetic and moderate intensity endurance training group and diabetic, and low intensity endurance training group, diabetic control and healthy control by using Kruskal-Wallis test indicated a significant difference between these groups (*P*-value:0.006).

**Conclusion:** Moderate and high intensity endurance training can significantly reduce the expression of RIP140 protein, and subsequently increase glucose uptake and ultimately reduce insulin resistance in diabetic rats.

**Keywords**: Metabolic syndrome, Body mass index, Physical activity, College students Seasons

## Introduction

Insulin sensitivity is key to the maintenance of systemic energy homeostasis (1). The inability of an individual to respond to insulin signals to remove glucose, i.e., insulin resistance (IR), is the hallmark of type 2 diabetes and can be caused by a variety of

factors (2). Type 2 diabetes mellitus is an increasingly prevalent metabolic disorder in which the combination of systemic insulin resistance and impaired insulin production by pancreatic β cells results in hyperglycemia. Insulin regulates plasma glucose levels by selectively increasing glucose uptake into fat and muscle and by inhibiting hepatic glucose production (3). Insulin-responsive glucose uptake is initiated by a PI3K-dependentsignaling cascade that stimulates trafficking of GLUT4 glucose transporters to the plasma membrane, allowing removal of excess glucose from the bloodstream (4).

The maintenance of energy homeostasis requires the regulated expression of gene networks that control metabolic functions in response to changing environmental conditions. Receptor-interacting protein 140 (RIP140), also known as NRIP1, is a multifunctional coregulator with a central role in metabolic tissues (5). RIP140 plays an important role in adipocyte and hepatocyte function (5,6), energy homeostasis (7) and reproduction (8), as well as a wide range of metabolic pathways such as glucose uptake, glycolysis, TCA cycle, fatty acid oxidation, mitochondria biogenesis and phosphorylation Oxidative and etc (8). Recent studies by Li Na Wei and her colleagues indicate that RIP140 may not only be a transcriptional coregulator but may also function in the cell cytoplasm. They have found that cytoplasmic RIP140 inhibits glucose metabolism by reducing insulin stimulated glucose transporter 4 (GLUT4) trafficking and glucose uptake (9).

The deletion of RIP140 increases the expression of enzymes involved in oxidative phosphorylation and fatty acid oxidation whereas the overexpression of this protein reduces the oxidative capacity of skeletal muscle (10). RIP140-null mice show that it plays a crucial role in the control of lipid metabolism in adipose tissue, skeletal muscle, and the liver and is essential for female fertility (11). Recent studies have shown that removing RIP140 in mice causes browning of white fat deposits. RIP140-null mice are extremely lean and exhibit resistance to obesity and hepatic steatosis a well as enhanced glucose tolerance and enhanced responsiveness to insulin compared with matched wild-type littermates fed a high-fat diet (3). It is particularly important to decipher whether the action of RIP140 either as a coactivator or as a corepressor can be regulated by environmental stimuli such as fasting, exercise, or high-fat diet, leading to activation of specific signaling pathways. It has been established that RIP140 acts as a transcriptional corepressor for nuclear receptors controlling energy homeostasis in the adipose tissue and skeletal muscle (12).

Chronic exercise training is a common approach utilized to optimize health and prevent disease. While the beneficial physiological adaptations to long term exercise are well established in many systems such as skeletal muscle, the specific alterations that occur in adipose tissue especially visceral adipose tissue under this condition are less clear (13). And mechanisms by which these various reported changes in lipolysis occur remains unclear (14,15). Many sources report enhanced stimulated lipolysis in adipocytes from endurance trained subjects that is attributed to alterations in the lipolytic cascade (16-20). For example, Shepherd and colleagues showed Increases in aerobic capacity and intramuscular triglyceride (IMTG) utilization are well-described adaptations to endurance training (ET) and contribute to improvements in insulin sensitivity (21). Researchers have shown that exercise improves catecholamines stimulated lipolysis in obese subjects (22-24). Although endurance or aerobic training is usually considered as the best way to improve insulin sensitivity, little attention is paid to intensity training (25).

Despite many gains in understanding the function and molecular mechanisms, especially RIP140, in the regulation of glucose hemostasis in skeletal muscle, a lot of questions still remain unresolved. Identifying regulatory mechanisms that improve the

metabolism of visceral adipose tissue can be beneficial in health and disease treatment. According to the above, it is assumed that endurance training with different intensities can reduce the content of RIP140 in visceral adipose tissue of diabetic Wister rats and improve insulin resistance. Therefore, the purpose of this study was to compare the effect of endurance training (low, medium and high intensity) on the expression of visceral adipose tissue RIP140 and insulin resistance in streptozotocin-induced diabetic rats.

## Materials and Methods

### Animals

This research was of experimental type**.** Animal procedures were approved by Shahrekord university ethics committee of animals (SKU: MP221/2013) and complied with the Guide for Care and Use of Laboratory Animals. The eight-week-old healthy male wistar rats (250± 40 gr) were used in the present study purchased from Pasture Institute (Tehran, Iran). The animals were housed two per polypropylene cages at a room temperature of 22°C with 12:12 h dark: light cycle (lightings were turned on at 8 PM and off at 8 AM) and 60% air humidity with free access to water and rodent pellet food. Rats were divided into the following five groups randomly: the low intensity training group (n= 8), moderate intensity training group (n= 8), high intensity training group (n= 8), diabetic control group (n= 8) and healthy non-diabetic sedentary group (n= 8).

Animal procedures were approved by Shahrekord university ethics committee of animals (SKU: MP221/2013)**.**

### Streptozotocin-induced diabetes

Diabetes was induced by intraperitoneal injection of a single dose of streptozotocin in a fasting condition (STZ, 55 mg/ body weight; Sigma, St Louis, MO, USA) (26). To reduce the effect of streptozotocin on beta cells 15 minutes before streptozotocin injection, 270 mg/ kg of nicotinamide saline mice was used (27). Rats in sham just received buffer. Two days after STZ injection blood was obtained from a small nick in the tail and measured with a glucometer (Optium Xceed). Rats with a glucose concentration exceeding 300 mg/ dL were considered as a hyperglycemic state (28). From the diabetic experimental group comprising 40 rats, four rats in whom diabetes was not induced and six rats in poor health were excluded.

### Experimental protocols and exercising program

Wistar rats carried out eight-week treadmill training with different intensities for 30 min/training and 4 days per week for 8 weeks on a standard treadmill for small rodents. Rats were divided into groups including low intensity training group (5-8 m/min, 50-60% VO2 max), moderate exercise intensity group (14-16 m/ min, 65-70% VO2 max), and high intensity exercise group (22-25 m/min, 80% VO2 max) (29). In addition, voluntary continuous exercise was induced by a 10-voltage electronic stimulator.

### Tissue collection

At the end of eight weeks of endurance training in order to rule out temporary training effects of last session, tissue sampling was conducted 48 h after last exercise bout. All rats were fasted overnight by removing food from the rat's cages 12 h prior to sacrifice. They were sacrificed for tissue collection by an intraperitoneal injection of ketamin (75 mg/ kg) and xylazin (25 mg/ kg). The slow-twitch soleus tissues were excised, frozen in liquid nitrogen and stored frozen at -80°C until further analysis. The serum glucose levels were measured by glucometer in Germany, by measuring the tip of the tail and serum levels of insulin with a rat specific ELISA kit (Insulin rat ELISA DEV8811) manufactured by Demeditec in Germany with a sensitivity of 0.1 ng/ mL and the insulin resistance index Using the formula

HOMA- IR= (fasting insulin (ng= ml) * (fasting glucose (mg= dl)/ 22·5

Was obtained (30).

## Western blotting

In order to analyses of visceral adipose tissue protein expression of RIP140 by western blot, approximately 50 mg of each visceral adipose tissue pieces was powdered with a pestle in liquid nitrogen and lysed using a 1 mL of phosphate-buffered saline (PBS). Tissue homogenates were centrifuged at 12000 rpm for 15 minutes at 4°C and supernatant was removed. Total protein content of the tissue extract was determined by the Bradford method using bovine serum albumin (BSA), 50 µg of protein was collected per sample, separated by SDS-PAGE in 8% polyacrylamide and electro transferred to poly vinylidene difluoride membranes. The membranes were incubated in blocking solution (5% milk) at room temperature for 2 hours. The membranes were then incubated with primary antibody including RIP140 (anti RIP140-rabbit polyclonal-ab3425) overnight at 4°C. After washing, the membranes were incubated with a goat anti-rabbit (Santa Cruz, USA). After this stage, the samples were covered with an ECL kit and the proteins were identified using the LI-COR Scanner.

## Statistical analysis

Data are reported as means ±standard error (SE) values. To compare groups, dependent variables were analyzed by One-way variance analysis and Kruskal–Wallis. The post hoc U Mann Whitney test was used to determine significant differences between groups. Statistical significance was set at *P*-value< 0.05.

## Results

The results of one-way ANOVA showed significant effect of exercise on insulin resistance values (*P*-value: 0.001), insulin resistance values increased in the diabetic control group compared with healthy nondiabetic sedentary group, and With increasing endurance training, the index of insulin resistance improved (Table 1).

Comparison of protein expression of RIP140 by using Kruskal-Wallis test in five groups showed a significant difference (*P*-value: 0.006) (Table 2). The U-Mann-Whitney test showed significant differences between the healthy control and high intensity training groups (*P*-value: 0.009), diabetic control and high intensity training (*P*-value: 0.009), and also diabetic control and moderate intensity training (*P*-value: 0.04), healthy control and moderate intensity training (*P*-value= 0.03), as

**Table 1. The baseline characteristics**

| GROUP | GLUCOSE mg/ dl | | INSULIN ng/ ml | | Insulin resistance | |
|---|---|---|---|---|---|---|
| | Mean | Standard deviation | Mean | Standard deviation | Mean | Standard deviation |
| **DHE** | 341.50 | 91.905 | 0.1213 | 0.009 | 1.82 | 0.4414 |
| **DME** | 323.13 | 148.619 | 0.1425 | 0.030 | 1.95 | 0.8496 |
| **DLE** | 497 | 25.439 | 0.1725 | 0.031 | 3.80 | 0.6882 |
| **DC** | 557.75 | 158.847 | 0.1925 | 0.036 | 4.83 | 1.2274 |
| **NS** | 156.25 | 22.946 | 0.4900 | 0.031 | 3.40 | 0.5204 |

NS :non diabetic sedentary group ǂDC :diabetic control group ǂDLE :diabetic and low intensity training group ǂDME :diabetic and moderate intensity training group ǂ DHE :diabetic and high intensity training group

**Table 2. Comparison of two to two with the Mann-Whitney test in RIP140 expression**

| Variable | GROUP | NS | DC | DLE | DME | DHE |
|---|---|---|---|---|---|---|
| **RIP140** | NS | | 0.59 | 0.24 | 0.03* | 0.009* |
| | DC | 0.59 | | 0.17 | 0.04* | 0.009* |
| | DLE | 0.24 | 0.17 | | 0.29 | 0.01* |
| | DME | 0.03* | 0.04* | 0.29 | | 0.59 |
| | DHE | 0.009* | 0.009* | 0.01* | 0.59 | |

NS :non diabetic sedentary group ǂDC :diabetic control group ǂDLE :diabetic and low intensity training group ǂDME :diabetic and moderate intensity training group ǂ DHE :diabetic and high intensity training group

well as low intensity training compared to high intensity training (*P*-value: 0.01). The results showed that RIP140 content in training groups was more likely to decrease with increasing exercise intensity than diabetic control group (Figure 1).

## Discussion

The purpose of this study was compare effect of different intensity endurance exercise (low, moderate, high intensity) on expression of RIP140 visceral adipose tissue and insulin resistance in streptozosin- induced diabetic rats. Findings showed insulin resistance index (HOMA-IR) in diabetic rats decreased by increasing intensity of endurance exercise. Decrease insulin resistance was significant in diabetic groups with high and moderate intensity, compare with diabetic control group, nondiabetic sedentary group and diabetic with low intensity exercise group (*P*-value≤ 0.05).

Researches have shown in streptozosin-induced diabetic treats of animals, damage of pancreas $\beta$ cells insulin secretion led to an acute decrease in insulin levels and HSL activity increase that has been observed muscle mass loss and reduce adipose in sever insulin depletion models (streptozosin-induced diabetic) (31). Possible reducing serum insulin and glucose mechanisms through endurance exercise can include increase carrier proteins of glucose (GLUT4), decrease secretion and increase cleaning free fatty acids, increase glucose delivery to the muscles tendency to available glucose. High intensity and long duration exercise increase insulin sensitivity possibly by increasing the transfer of glucose to the muscle or reducing fatty acids synthesis and glucose reabsorption due to skeletal muscles activity (32). Also decrease in fat mass can be another reason of reducing insulin (33). Mast studies reported this decrease index following exercise schedule, have had a relatively high intensity exercise (34,35). According to these cause, the reduction insulin resistance in this study seems logical. Contradiction in studies results can be caused by different factors such as nutrition type, exercise program, subjects type and intensity and duration of exercise.

The significant difference observed in RIP140 expression in healthy nondiabetic sedentary and diabetic control rats compare with high and moderate intensity endurance exercise diabetic groups can be justified by effort of anti-consumption energy and insulin sensitivity of the RIP140 nuclear by inhibition involved genes in mitochondrial biogenesis, β-oxidation of FA, oxidative phosphorylation, glycolysis and the TCA cycle as well as inhibition of GLUT4 gene expression in the

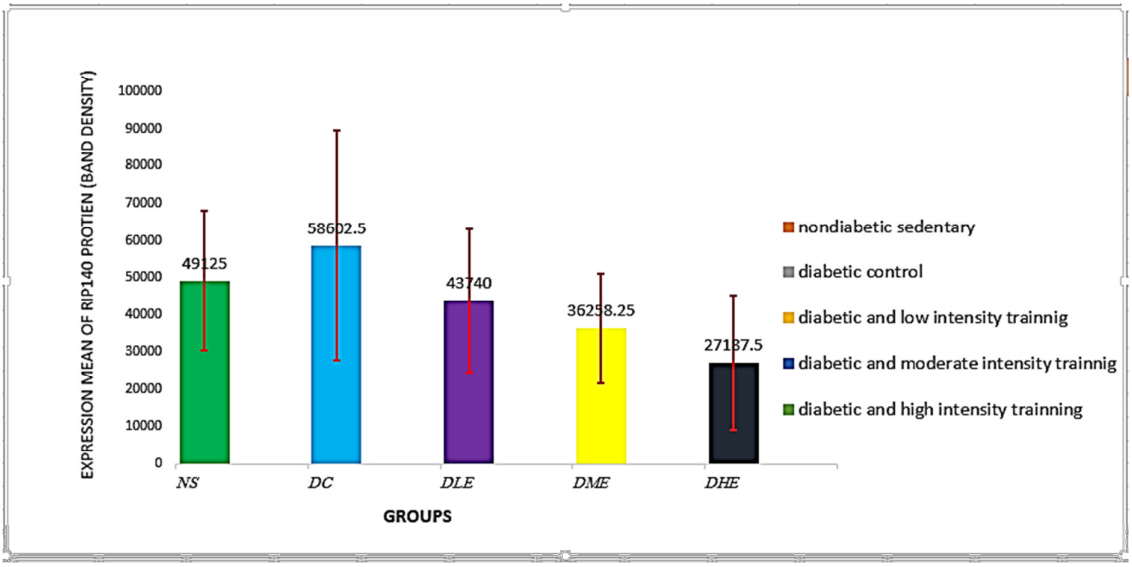


**Figure 1. Changes in expression of RIP140 in groups**

nucleus in the one hand and inhibition of the transfer of GLUT4 from the cytoplasm to the membrane by interaction with the AS160 on the other hand (36). It seems logical that RIP140 expression decrease through endurance exercise in diabetic rats lead to increase GLUT4 transfer and As a result, increased adipocyte insulin sensitivity. However other inferred factors are mentioned that increase insulin sensitivity in diabetic patients such as increasing the expression of PGC-1α through exercise training by increase mitochondrial biogenesis and adipocytes oxidative capacity and also increase adiponectin expression (37).

Also there was observed a significant difference of RIP140 expression in low intensity training group, compare with diabetic and high intensity training. So the amount of RIP140 was less in high intensity training group. It seems the non-significant increase of RIP140 in diabetic control rats compare to healthy nondiabetic sedentary group in partly decreased by endurance exercise to prevent destructive effects of GLUT4 transfer decrease and consequently from insulin sensitivity decrease. Studies demonstrated RIP140 expression is regulated by estrogens (38), retinoic acid (39), progesterone (40), and androgens (41). ERRs involved in controlling energy metabolism also modulate RIP140 transcription (42). Recently it has been determined that micro RNAs regulated RIP140 expression (43). It looks the exercise caused RIP140 decrease in diabetic rats by change in this factor. As that, chang et al (2010) and Seth et al (2007) demonstrated RIP140 less response to exercise compare with control group may be related to ERRs and PGC-1α inhibition effects (10,44). Eva-Karin Gidlund (2015) there was no significant difference in RIP140 mRNA levels of skeletal muscle between exercise group and control group. The lower levels of RIP140 in EXG compare with CG may be represent muscle contraction that reduces inhibition effects of RIP140 on oxidative system so make us suppose RIP140 inhibition actions are suppressed (45). The result of the study is consistent with the present research. Stepto et al (2012) showed for the first time that acute exercise increased RIP140 protein expression in skeletal muscle homogenates immediate after exercise and after 3 h of recovery (46). Fan et al (2017) showed while exercise does not affect RIP140 expression, it induces its translocation from the nucleus to the cytoplasm, thereby decreasing its repression of target genes (47). Hood et al (2011) reported total RIP140 in skeletal muscle biopsy samples don't decrease after high intensity training and there were no effects of training on RIP140 protein content (48). Edgett et al (2013) demonstrated RIP140 mRNA expression in skeletal muscle increase is independent of the intensity of exercise and occurs in all intensity (49). Serpiello et al (2011) did not find any increase in the abundance of RIP 140 protein after acute or chronic repeated sprint exercise (50). Adeel safdar et al (2011) showed Endurance exercise abrogated the nuclear accumulation of RIP140 (51). Pu-Ste Liu et al (2014) demonstrated RIP140 expression in macrophage of adipose tissue are increased by high-fat diet and RIP140 expression decrease in monocytes/ macrophages improve insulin resistance caused by high-fat die (52). The results of the researches are inconsistence with this study. Observed differences in some of this studies may be relevant to difference of type of tissue (adipose or muscle), type of fat stores (visceral or subcutaneous), type of exercise (acute or chronic), exercise protocol (duration and intensity), subjects (human and animal), type of subjects (healthy or patient) and measurement method.

## Conclusions

It seems increasing intensity of endurance exercise training let to more decrease in RIP140 expression in diabetic rats so decrease of RIP140 caused to increased transfer of GLUT4 to adipocyte membrane by increase inactive AS160 that occurs by AKT (11). It is likely that appropriate intensity of exercise increase insulin sensitivity by RIP140 decrease

and so increase transfer of GLUT4 and increase glucose uptake in rats. Generally may be this proteins can be suitable target for insulin resistance treatment and its related complication.

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## Conflict of Interest

There is no conflict of interest to be declared.

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