



Aerobic Exercise-Induced Weight Reduction Decrease Serum Leptin in Patients with Diabetic Mellitus

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ABSTRACT

It is generally accepted that peptides secreted by adipose tissue have a key role in obesity and related disorders such as diabetes. This study aimed to assess effect a chronic aerobic exercise on serum leptin level in type 2 diabetes patients.

Thirty-four adult obese male with type 2 diabetic participated in the study that designated as exercise group, or to the control group. Fasting blood samples were collected from brachial vein of all patients in control and exercise groups for measuring serum leptin, insulin, glucose and insulin resistance before and after a 3 month aerobic exercise. Anthropometrical indexes also measured in two groups. Data were analyzed by A T-test method in SPSS software version 15. A p-value < 0.05 was considered to be statistically significant.

The statistical finding of independent T-test show that, there is not difference between the baseline level in all biochemical and anthropometrical variables in two groups ($p \geq 0.05$). Aerobic exercise led to decrease in serum leptin, glucose, insulin resistance, body fat percentage, weight, and waist circumference and body mass index in exercise group ($p < 0.05$). There was not any significant change in all variables in control groups after detraining ($p \geq 0.05$).

Based on this data, it was concluded that serum leptin and determinative markers type 2 diabetic improve in relation to chronic aerobic exercise that are accompanied with decrease in anthropometrical indexes.

Keywords: Diabetes mellitus, Leptin, Weight loss

INTRODUCTION

Type 2 diabetes is the most common endocrine and metabolic diseases in throughout worldwide which involves 30 to 40 percent of obese people [1]. While the mechanisms responsible for the prevalence of type 2 diabetes in obese people are not fully recognized yet, the possible role of leptin in the prevalence of this disease has been repeatedly considered [2]. Leptin is a peptide hormone derived adipose tissue with molecular weight of 16 kDa whose concentration varies depending on the body fat levels and affects glucose metabolism and insulin sensitivity [3]. Although the main mechanisms of Type 2 Diabetes appearance are not fully recognized yet, the role of obesity in the appearance of this disease has been repeatedly proven [1]. Obesity is associated with increase in blood leptin levels. Some scientific sources have reported that leptin did not inhibit glucose-related insulin secretion [4]. But other research findings have revealed that leptin resistance is one of the factors affecting hyperinsulinemia and ultimately glucose intolerance in obesity or its related diseases [2]. Some studies also mention that there are leptin receptors in pancreatic beta cells and play an important role in insulin secretion from these cells [5]. The presence of hyperglycemia and hyperphagia in obese individuals, despite high levels of insulin and leptin, suggests these individuals are resistant to the actions of both hormones [6]. Some findings state indicates that leptin can also exert peripheral actions independent of its effects in the hypothalamus [7]. For example, studies have mentioned the inhibitory effect of leptin on insulin gene expression as well as insulin secretion from pancreatic beta cells in humans and animal models [7, 8].

Apart from its acute effect on insulin secretion from beta-cells, leptin also inhibit proinsulin gene expression beta-cells proliferation in both humans and animals, although the main mechanisms responsible for that have still remained unknown [9]. Negative relation between plasma leptin levels with insulin sensitivity has been also reported in some studies even after adjustment for adiposity [10]. Some studies have reported decrease [11], increase or no change [12] in leptin levels in diabetic patients compared to healthy people. Besides genetics, multiple risk factors such as age, weight gain, especially adipose tissue levels and inactivity and lack of physical activity, especially in obese people after 30 years old, are considered of the main causes for occurrence of insulin resistance and type 2 diabetic [13]. Meanwhile, health science professionals' focuses on the role of exercise therapy and physical activity independently or along with other medicinal treatments, to prevent type 2 diabetes

and metabolic and hormonal factors affecting its occurrence. The Effect of exercise on leptin concentration is still controversial. Some studies have reported that the exercise leads to leptin reduction depending on duration and energy expenditure. For example, in a recent study, 30 minutes exercise in % 80VO₂max led to significant reduction in serum leptin [14]. Fatouros et al (2005) also reported a decrease in plasma leptin concentration after resistance training (6 months, 3 days/week, 10 exercises/three sets) in fifty inactive men [15]. While, several studies have suggested no change in leptin levels by difference exercise training. In this regard, the findings of a recent study have reported no change in serum leptin following 60 minutes of treadmill exercise at 50% of VO₂max in 6 healthy untrained males [16]. Also Kramer et al (1999) was observed insignificant change in serum leptin levels after 9 weeks of aerobic exercise [17].

Reviewing the findings regarding the effect of exercise program on leptin levels in obese people or type 2 diabetic patients, shows that results are conflict and controversial. Hence, the present study is conducted aimed to determine the effect of a three-month aerobic exercise program on serum leptin and insulin resistance in type 2 diabetic patients.

MATERIALS AND METHODS

The objective of study was to assess effect a chronic aerobic exercise program on serum leptin, fasting glucose, insulin resistance and anthropometrical indexes in type 2 diabetic patients. In fact, this semi-experimental study was conducted in order to determine the effect of a merely exercise program in the absence of a control diet on serum leptin levels and the other variables in these patients.

Subjects: The present study was approved by the ethic committee of Islamic Azad University. Thirty-four adult obese male with type 2 diabetic that divided to control and exercise group participated in the study. Subjects ranged in age from 35 to 50 y and body mass index 32.88 – 2.44 kg/m² (Table 1). After the nature of the study was explained in detail, informed consent was obtained from all participants.

Inclusion and exclusion criteria: A medical history to retrieve information about health status, current medications and activity/diet history were collected of all patients. Subjects with a history or clinical evidence of recent myocardial infarction, congestive heart failure, active liver or kidney disease, growth hormone deficiency or excess, neuroendocrine tumor, anemia were excluded. Participants were included if they had not been involved in regular physical activity or diet in the previous 6 months. All subjects were non-smokers. Nutritional status of two patients groups was similar during the time before the study. The participants of two groups were asked to remain their diet during the study. Those patients who were not able to avoid using hypoglycemic drug for 12 hours before blood sampling were excluded.

Anthropometrical measurements: Data regarding height, age and anthropometrical indices were measured and recorded in Physiology Laboratory of the Saveh University. Height was measured with Seca height rod (0.5 accuracy), without shoes, and weight with Seca weight scale (100 g accuracy), with light clothes and without shoes. Waist circumference was measured after a normal expiration under the midline of the subject's armpit, at the midpoint between the lower part of the last rib and the top of the hip. Percentage of fat (%fat) was assessed with a body composition monitor (OMRON, BF508, Finland). Resting heart rate of all patients was measured after 10 minutes of rest.

Blood sampling and exercise program: After measuring the anthropometrical indexes, fasting blood samples were collected from brachial vein in sitting position after a 12-h overnight fast of all patients in control and exercise groups for measuring serum leptin, insulin, glucose and insulin resistance. Serums were immediately separated and stored at -80° C until the assays were performed. All patients and healthy individuals were recommended to avoid participating in any exercise for 48 hours prior to blood sampling.

After the blood sampling, diabetic patients of exercise group participated in a three-month aerobic exercise program, three times per week with exercise intensity from 60 to 80 of maximal heart rate for each subjects, so that exercise intensity was the lowest in the first sessions and gradually duration and exercise intensity were increased in coming sessions. Exercise programs were conducted in accordance with the instruction of the America Diabetes Association [18]. Each session was started with warm-up phase, then aerobic activities in the form of running on a treadmill and then ended by cool up. Target heart rate and exercise intensity were monitored by polar telemetry. Diabetic control group did not participate in the exercise program during this three-month period. Finally, fasting blood

sampling repeated at 48 hours after the latest session of all patients in control and exercise group patients. In addition, resting heart rate and anthropometrical indexes measured after exercise program.

Biochemical analysis: Plasma glucose was determined by enzymatic (glucose oxidase-amino antipyrine) colorimetric method (Pars Azmoun, Tehran, Iran), the Intra-assay and inter-assay coefficient of variation and sensitivity of the method were 1.74%, 1.19% and 5 mg/dL, respectively. The blood samples centrifuged immediately at 2,000 rpm for 10 min and then serum were stored at -80°C until analysis was performed by ELISA method. Serum insulin (Demeditec Company, Germany) and leptin (Biovendor Company, Czech) was determined by ELISA method. The Intra- assay and inter-assay coefficient of variation and sensitivity of the method of insulin were 2.6%, 2.88% and 1.76 $\mu\text{IU/ml}$ respectively. Also, The Intra- assay and inter-assay coefficient of variation and sensitivity of the method of leptin were 6.7%, 4.2% and 0.2 ng/ml respectively. Insulin resistance was calculated in each patient by using fasting insulin and glucose values [19].

Statistical analysis: Statistical analysis was performed with the SPSS software version 15.0 using a T-test method. A p-value < 0.05 was considered to be statistically significant.

RESULTS

In the present study, the effect of a three-month aerobic exercise program on serum leptin levels, insulin resistance and blood glucose were studied in type 2 diabetic patients. Mean and standard deviation in before and after exercise intervention in each variable are summarized in table 1. Findings from independent T-test showed that there is no significant difference in baseline levels of serum leptin, fasting glucose, insulin and insulin resistance as well as anthropometrical indexes between exercise and control groups of the studied patients. Main finding of this study was significant decrease in serum leptin levels by aerobic exercise program in exercise group ($p = 0.023$, Figure 1). Exercise program led to significant weight loss in exercise group ($p = 0.009$). Also, the exercise led to the significant decrease in each one of the anthropometrical indexes such as abdominal circumference, body fat percentage, body mass index ($p < 0.05$, Table 1). The resting heart rate of the exercise group patients decreased significantly compared to before exercise intervention ($p = 0.000$). Statistical findings showed a significantly decrease in fasting glucose concentration ($p = 0.000$, Figure 2) and insulin resistance ($p = 0.038$, Figure 3) in exercise group. Although reduction in insulin resistance had a linear relationship with decrease in serum leptin levels, this relationship was not significant ($p \geq 0.05$). In response to aerobic training program, changes in serum leptin was positively correlated with changes in BMI ($r = 0.56$, $p = 0.021$, Fig 4) and body fat percentage ($r = 0.51$, $p = 0.02$). On the other hand, the statistical findings show that all anthropometrical and biochemical remained without change in control group ($p \geq 0.05$).

Table 1: Mean and standard deviation of anthropometrical and biochemical variables of healthy and diabetic groups in baseline and after intervention

Variables	Groups	Control diabetic		Exercise diabetic	
		Pretest	post-test	Pretest	post-test
Age (year)		42 \pm 8	42 \pm 8	43 \pm 6	43 \pm 6
Height (cm)		174 \pm 8	174 \pm 8	173 \pm 5	173 \pm 5
Weight (kg)		99 \pm 6	100 \pm 8	98 \pm 7	91 \pm 8 *
Systole (cmHg)		14.21 \pm 1.71	13.90 \pm 2.68	13.65 \pm 2.44	12.08 \pm 1.67 *
Diastole (CmHg)		8.96 \pm 1.91	7.82 \pm 2.14	8.5 \pm 0.98	8.16 \pm 1.75
Waist circumference (cm)		106 \pm 10	107 \pm 9	107 \pm 11	101 \pm 12 *
Hip circumference (cm)		104 \pm 12	104 \pm 9	103 \pm 9	100 \pm 11 *
Waist to hip ratio		1.02 \pm 0.11	1.03 \pm 0.09	1.04 \pm 0.12	1.01 \pm 0.13 *
BMI (kg/m ²)		32.70 \pm 3.21	33.02 \pm 3.11	32.74 \pm 2.46	30.40 \pm 2.95 *
Body fat (%)		28.63 \pm 2.42	28.94 \pm 3.11	29.01 \pm 2.28	24.11 \pm 4.62
Heart rate (bpm)		85 \pm 7	86 \pm 9	84 \pm 11	76 \pm 7 *
Glucose (mg/dl)		228 \pm 47	232 \pm 48	236 \pm 39	187 \pm 31 *
Insulin ($\mu\text{IU/ml}$)		8.67 \pm 2.11	8.38 \pm 2.32	8.93 \pm 2.16	8.88 \pm 2.14
Insulin Resistance		4.88 \pm 1.12	4.80 \pm 1.34	5.20 \pm 1.68	4.10 \pm 1.72 *
Leptin (ng/ml)		7.26 \pm 2.03	7.62 \pm 2.42	7.63 \pm 1.39	5.21 \pm 2.03 *

- Data represent means \pm SD

- * represent significant changes compared to pretest levels ($p < 0.05$).

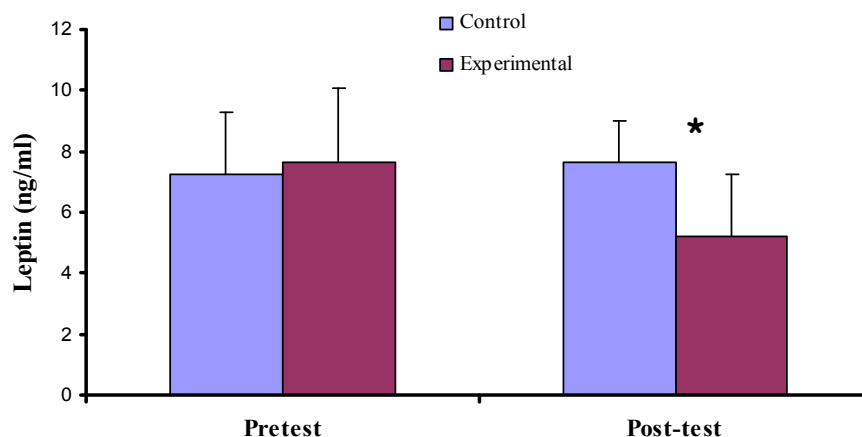


Figure 1: The changes pattern of serum leptin concentration in control and exercise groups of diabetic patients. Aerobic exercise leads to significant decrease in serum leptin in exercise group, while this variable remained without change in control group

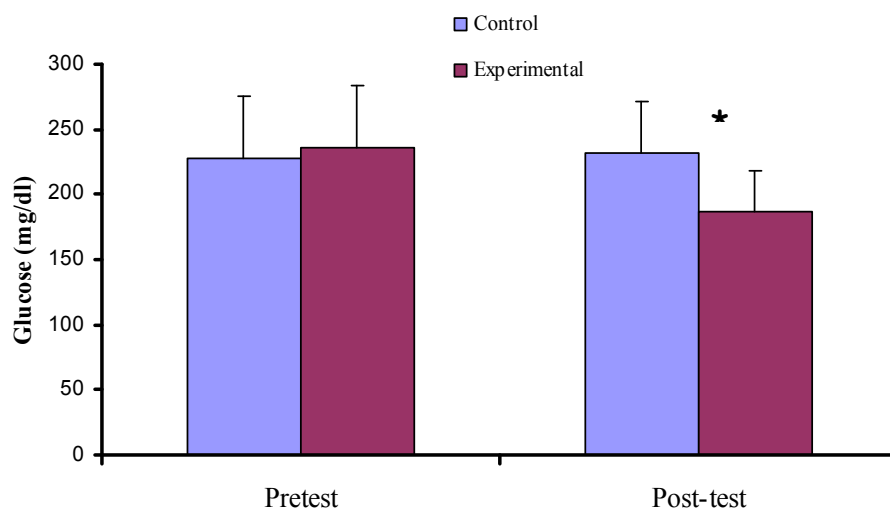


Figure 2: The changes pattern of fasting glucose concentration in control and exercise groups of diabetic patients. Aerobic exercise leads to significant decrease in fasting glucose concentration in exercise group, while this variable remained without change in control group

DISCUSSION

This hypothesis is raised that some peptide hormones such as leptin or adiponectin, independent of anthropometrical variables (age, sex, body fat, fat-free mass), affect insulin sensitivity and are appropriate predictor of insulin sensitivity [20]. Stress, nutrition, body composition and physical activity level in humans, affects the prevalence of type 2 diabetes and its effective components [21]. Since the short or long-term exercise affects body composition and carbohydrate and fat metabolism, it is particularly important to investigate the effect of exercise on circulation leptin levels and other peptide hormones affecting the energy balance and glucose homeostasis [22]. Thus there is controversy regarding the role of leptin in diabetes. Our study findings showed that three-month aerobic activity leads to decrease in serum leptin in type 2 diabetic patients. Leptin, the product of the *ob* gene, plays a key role in the regulation of body weight. The discovery of leptin has led to numerous experiments to better understand its function, and many of these studies have focused on leptin's response to both acute exercise and exercise training. To support of our findings, some studies which

have improved the physical fitness level and have affected body composition have been associated with decrease in levels of plasma leptin [22].

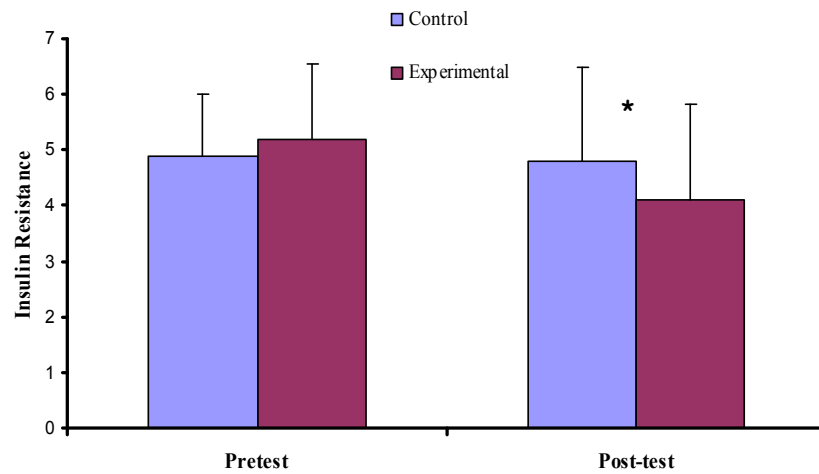


Figure 3: The changes pattern of insulin resistance in control and exercise groups of diabetic patients. Aerobic exercise leads to significant decrease in insulin resistance in exercise group, while this variable remained without change in control group

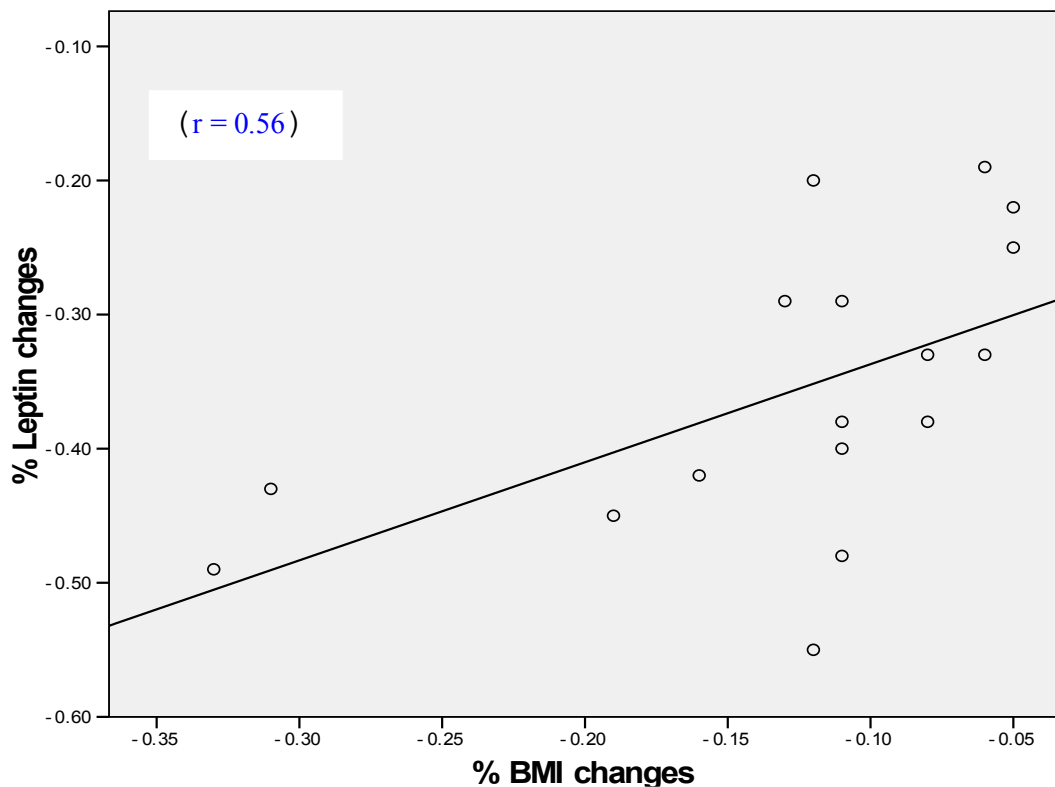


Figure 4: A significant positive correlation was observed between the changes in serum leptin and BMI in response aerobic training program in diabetic patients.

Some researcher allotted this decrease to the rise in the catecholamines and hypoinsulinemia induced by exercise [23]. But Contrary to these results, Landt *et al.* (1997) reported an 8% insignificant reduction in fasting serum leptin concentrations after 2-hours of cycling exercise [24]. In another

study, no significant changes were observed in blood leptin levels despite the increase in insulin sensitivity following with 60 minutes of aerobic exercise for 7 weeks [25]. These findings were also observed in other studies with different intensity and duration of exercise [17, 26]. But in most studies, long-term exercise which has significantly decreased body fat levels has also been associated with decrease in blood leptin levels [27, 28]. In another study, a decrease in plasma leptin concentration observed after resistance training (6 months, 3 days/week, 10 exercises/three sets) in fifty inactive men and this decrease was accompanied by a reduced skin fold sum and BMI [15]. Adipose tissue especially abdominal fat has a special role in blood leptin levels [19]. In obese individuals, increase in adipose tissue is associated with hyperleptinemia and increase in leptin resistance and suggests a negative relationship between leptin and insulin sensitivity [29]. Circulating leptin concentrations reflect the amount of adipose tissue in the body. Interventions that decrease body weight and/or fat may decrease leptin levels. Those exercises training that eliciting significant energy expenditure may decrease plasma leptin [30]. Generally, based on this data, it was concluded that only exercise training can decrease serum leptin that exercise duration is longer than 12 weeks or is associated with at least 5% reduction of body weight and body fat [31,32]. Our study also show that decrease in serum leptin levels was associated with significant decrease in body weight, abdominal circumference, body mass index, body fat percentage and insulin resistance. So that, changes in serum leptin was positively correlated with changes in BMI. In fact, decreased serum leptin after training was most strongly related to decreased BMI or body fat percentage. To support our findings, the studies on obese males or females showed that decreases in leptin concentrations after long-term aerobic exercise program were associated with fat mass loss [28], BMI and percentage body fat [15, 22, 27] thus may improve the leptin resistance. In other words, three months aerobic exercise resulted in reduction of anthropometrical indices and insulin resistance in type 2 diabetic patients. Exercise training increases total energy expenditure by up regulating the direct energy cost of physical activity, which may lead to decreased body fat stores that ultimately will depress leptin secretion [33]. It is generally accepted that leptin is mainly secreted from adipose tissue. Therefore, exercise training protocols that result in reduced fat mass are generally accompanied by lower leptin concentrations. Reductions in leptin levels have also been attributed to alterations in energy balance, insulin sensitivity and lipid metabolism. Some study suggested that this response could be partially due to a rise in the norepinephrine appearance rate [34].

In diabetic patients, plasma leptin levels are confounded by factors that affect insulin sensitivity and insulin secretion such as hypoglycemic drugs and diet [35]. The presence of the leptin receptor in pancreatic cells [36] indicates that leptin might be alter insulin secretion in states of increased fat depots and decreased insulin sensitivity. Leptin acutely inhibits glucose-stimulated insulin secretion in rats [37]. In human obesity such as type 2 diabetes patients, high leptin levels are associated with leptin resistance [38] and, therefore, leptin resistance might also exist in pancreatic islet cells leading to a loss of the repressive control of insulin secretion by leptin [39]. Some studies have also pointed that Levels of circulating leptin are negatively associated with insulin sensitivity even after adjustment for adiposity [10].

In the present study, although changes in insulin resistance were not related with changes in serum leptin, the exercise resulted in the significant reduction of insulin resistance. On the other hand, some scientific resources suggest that, decrease in leptin concentration in diabetic patients is possibly due to reduction of glucose after exercise in addition to the negative energy balance [40]. Researchers have considered not only the effects of the exercise stress on serum leptin, but the combined effect of energy availability. These authors concluded that apart of exercise training, diurnal variation in leptin levels was dependent upon energy and carbohydrate availability [40]. This hypothesis is raised that decrease in blood glucose leads to decrease in leptin secretion from adipose tissue [41, 42].

In support for these findings, the significant reduction of both fasting glucose and blood leptin was observed in this study subsequent with workout and the significant correlation was observed between decrease in serum leptin and blood glucose due to three months workout program. With regard to our findings, so we can conclude that reduction of leptin by exercise will be affected circulating glucose. Because, some studies have also pointed out that the presence of leptin in the liver has direct effects on gluconeogenesis that affect blood glucose concentration [43]. The amount of glucose taken up by adipocytes is proportional to the secretion of leptin in cultured cells. Mueller states that an increase in glucose uptake into the muscles during the post-exercise period, thus potentially limiting glucose

availability to the adipose tissue lead to reduction in leptin secretion [44]. In a study observed that, the infusion of small quantities of glucose to fasted human prevents the decline of glycemic and prevented the decrease in leptin levels [41]. In type 2 diabetic patients, decrease in glucose uptake by adipose tissue can be a justification for fourfold reduction of leptin levels Compared with normal human after exercise [44]. Despite these findings, some studies have reported leptin concentration decrease after long-term exercise in the absence of weight loss or independent of weight changes or body composition [23, 45].

In conclusion, our findings in support for some other studies indicate that the long-term aerobic exercise that accompanied with reduction in body fat levels and insulin resistance, leads also to reduction of serum leptin levels. Since the diet in both groups was similar before the study and all participants were asked to remain their diet during the study, so we conclude that decrease in leptin and other variables can be attributed to aerobic training intervention. Based on this data, it was concluded that Aerobic exercise-induced weight reduction decrease serum leptin in patients with diabetic mellitus.

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Conflict of interest

The authors declare that they have no Conflict of Interests.