

The Effect of Resistance Exercise on Blood Glucose, Insulin and Insulin resistance in Iranian Patients with Type II Diabetes: A Systematic Review and Meta-Analysis

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Abstract

Objective: Resistance exercise is recommended as effective treatments for people with type 2 diabetes. However, the impact of this mode of exercise on blood glucose, insulin and insulin resistance in Iranian's type 2 diabetic patients is unclear. We conducted a systematic review of the literature for the effect of resistance exercise training on these clinical markers in Iranian's type 2 diabetic patients.

Materials and Methods: Electronic databases including Sid.ir, magiran.com, PubMed, Google scholar, Embase, Medline and science direct were investigated and searched for persian and english articles, published before July 2017, which performed in Iran. Standardized mean difference (SMD) with a 95% confidence interval (CI) was calculated to assess this association. Of 99 articles retrieved, 9 met our inclusion criteria and were included in the meta-analysis model. Data analysis were done using STATA software version 12.0 and $P \leq 0.05$ was set as statistical significant.

Results: The results indicate that there were significant association between resistance training and blood glucose levels ($P=0.0001$; -1.367,-0.756; 95%CI), insulin ($P=0.0001$;-0.904,-0.313; 95%CI) and insulin resistance ($P=0.0001$;-1.006,-0.366; 95%CI).

Conclusion: This meta-analysis showed that resistance exercise training program in patients with type 2 diabetes has a significant effect on glycemic control. It is recommended that sport and medicine experts use resistance exercise as a non- pharmacological intervention for treatment of type 2 diabetes patients. Future long term studies focusing on patient-relevant outcomes are warranted.

Keywords: Type 2 diabetes, Insulin, Insulin resistance, Glucose, Resistance training, Meta-analysis

Introduction

Diabetes is the most common form of endocrine disorders and is currently a major worldwide cause of morbidity and mortality which is the 7th known cause of the death in the world (1). Type 2 diabetes is a metabolic disorder which is appeared along

with chronic hyperglycemia and disorder in the metabolism of glucose, protein and lipid which leads to many pathological changes such as neuropathy, nephropathy, retinopathy, immune system defect and vascular damages (2). In resistant patients to the insulin, reduction in the sensitivity of lipid cells to the insulin hormone causes the increase of free fatty acids in blood which is one of the predominant signs of type 2 diabetes and it gradually expands the resistant to insulin and inefficiency of pancreas Beta cells (3,4). Resistance to insulin is a metabolic situation in which the rate of tissues response to the physiological values of insulin are lower than normal (5). In fact, resistance to insulin is a situation in which body's cells become resistant against insulin effects (4,5). Resistance to insulin exhibits a big defect in maintaining the normal level of blood glucose (5) which is often accompanied to the metabolic and cardiovascular diseases include type 2 diabetes, intolerance of glucose, obesity, hypertension, arteriosclerosis (5,6). These diseases are related to the high rates of insulin which is induced by resistance to insulin (6). Recently, resistance exercises have been presented as the effective curative tools in many chronic diseases treatments like type 2 diabetes (7). According to the studies, resistance exercise can improve the volume, strength and power of the muscle (8). Hence it is applied as a healthy medical tool in elderly patients (8-10). Resistance exercise improve glycemic control and decrease resistance to insulin and increase muscle strength is patients with diabetes (11). Resistance exercise can increase insulin sensitivity and daily consumption of energy (11). Some evidence have shown that the intensity variable in resistance exercise is more important than the exercise volume in the treatment of patients with type 2 diabetes and it is efficient in improvement of insulin resistance, metabolic control and cardiac function in these patients (12). Long term resistance exercise improves tolerance to glucose or sensitivity to insulin of the body and it is accompanied by the increase

in the skeletal muscle volume and increases the glucose storage in the body (13). Even in some studies it has been reported that resistance exercise is more useful than endurance exercise to control blood glucose and increase in sensitivity to insulin in patients with type type 2 diabetes (14). Ibans et al (2005) reported that 16 weeks of resistance exercise causes 43% increase in insulin function and 7.1% reduction in the level of plasma glucose (15). Hordern et al (2011) through a study on 34 patients with type 2 diabetes found that the response to changes in glucose concentration in the first week of exercise (13.3% reduction) compared to the fourth week (22.8% reduction) has been lower. It indicates the positive effects of exercise with its continuity (16). In general, the meta-analysis studies results from the outside of Iran have shown that anaerobic or resistance exercise can improve glycemic index controls in patients with type 2 diabetes (17-19). For example, in a study by Boule et al (2001) 14 articles had been systemically reviewed and underwent meta-analysis from which 12 cases have had used aerobic and 2 cases resistance exercise. The results of this study shows that exercise can lead to control blood glucose and hemoglobin A1c (HbA1c) reduction in patients with type 2 diabetes. In addition, the meta-analysis results by these researchers show that sport and exercise can reduce abdominal obesity and aggregation index of the body in patients with diabetes type 2 (17). Up to now, no study has been conducted to sum up researches inside Iran. Of course, it can't speak about the effects of resistance exercises on the improvement in risk factors associate to the disease among Iranian society. Therefore, the primary objective of the current study was to systematically review and, if appropriate, perform a meta-analysis of studies directly comparing resistance exercise interventions of different intensities on HbA1c, insulin and insulin resistance index in Iranian people with type 2 diabetes.

Materials and Methods

Search strategy

In this study the information base SID and Magiran and also scientific publication system confirmed by ministry of science and ministry of health had been searched from 2001 to 2017, aimed to find Persian resources related to the topic. Furthermore to find articles published by Iranian authors in English-language journals, Scopus, Google Scholar, PubMed and Science direct databases were also searched. References in all articles and reports which had been found in the above electronic search were evaluated manually to find other probable resources. Extracted data included general information about the systematic review (e.g. year of publication, origin, journal, and sources of funding) as well as specific details about the participants, interventions, comparison groups, and outcomes (PICO) of the studies included in the reviews. Key words used for searching databases selected from medical topical headings MESH were: "type 2 diabetes" in combination with "diabetes" and "resistance training" and "physical activity" and "Insulin resistance" and "insulin" and "fasting blood glucose".

Selection Criteria

To be included in the analysis, studies had to meet the following criteria: 1) Original scientific articles; 2) Their sample had been chosen among more than 18 years old subjects; 3) Articles whose sample had merely been derived from human subjects; 4) The studied samples had no other disease except type 2 diabetes and 5) Articles which had studied long term respond of exercise activities without consuming any dietary supplements at least for 8 weeks. Articles that had the following characteristics were also excluded from the study: 1) reviewed studies (20,21); 2) studies that examined the effects of exercise with the use of a specific drug or a specific nutritional supplement (22); 3) The exercise program did not have the necessary physiological qualities (23); 4) the studies

lacking the control group; 5) the assessed samples were the same or repeated the studies performed with the previous data (24-29). Finally, 9 eligible articles (30-38) were selected to perform the current meta-analysis (Figure 1). Finally, the selection of articles was based on an independent view of the three researchers specializing in the topic. This process was such that the condition for the entry of the articles to the present study was initially based on the expertise of these three researchers, and eventually by all other investigators, all of these items were monitored.

Data extraction and evaluation of the quality of studies

Information about the name of the first author, publication year, the site of study, sample volume, gender of participants, the rate of variables like insulin sensitivity, insulin, fasting blood glucose from control and experimental groups, type of resistance exercise accompanied by its intensity, duration and frequency in a week, sampling method and period of diabetes infection have been extracted from articles (Table 1). The estimation of bias risk was also been conducted based on Cochrane Risk of Bias tool (39). Cases which were studied in this tool include: the hierarchy of subjects classifications in control and experimental groups, participants, researchers and lab personels unawareness of the studies implementation trend, reporting selected results and other probable resources of bias. Data extraction and evaluating the quality of studies were also been carried out by two authors (Dr. Masoud Rahmati and Dr. Mohammad Fathi) and any differences between the two authors had been controlled by an impartial researcher (Dr. Rahim Mirnasuri).

Statistical Analysis

In this meta-analysis, the relationship between resistance exercise and fasting blood glucose, insulin and insulin resistance to it in the

Table 1. Characteristics of the investigated studies in present study

Author (year)	City	Sex	Age range (year)	Duration of diabetes (year)	Total number (n)	Type of exercise	Training period (week)	Repeat the exercise (session per week)	Training intensity (1RM)	Sampling
Afshonpour et al (2016)	Ahvaz	Men	30-50	1	27	Circular resistive training	8	3	30-70	Purposive sampling
Azarmehrer et al (2016)	Amol	Women	50>	2	20	Circular resistive training	8	3	60-80	Purposive sampling
Tashakorzadeh et al (2016)	Zahedan	Women	50>	3	18	Resistance training (weight and device)	10	3	30-80	Purposive sampling
Nazem et al (2015)	Hamadan	Men	50>		32	Weight training Practice with dumbbells	10	3	40-75	Simple random sampling
Bahari et al (2014)	Esfahan	Women	44-69		20	Practice with the device	8	3		Purposive sampling
Tofighi et al (2013)	Urmia	Women	50>	1	26	Circular resistive training	12	3	40-60	Purposive sampling
Saghebjo et al (2013)	Qaemshahr	Men	45-60	1	18	Circular resistive training	8	3	60-80	Purposive sampling
Amouza et al (2012)	Qaemshahr	Men	50>	1	18	Circular resistive training	8	3	50-80	Purposive sampling
Amini Lari et al (2017)	Shiraz	Women	45-60	2	27	Resistance training	12	3	50-55	Simple random sampling

1RM: One-repetition maximum.

conducted studies inside Iran had been examined. All variables from experimental and control groups were calculated using the standardized mean difference (SMD) with the coefficient 95% confidence. To determine heterogeneity of studies Chi-square and I square tests were used (evidence for heterogeneity of $I^2 > 50\%$, $P < 0.05$). If any heterogeneity was observed in studies, the Random-effects model and otherwise, the Fixed-effect model were used. Sensitivity analysis was used to assess whether the results of meta-analysis were affected by study or specific studies. Also, the bias in the articles publication was examined using the evaluation of the funnel plotted diagrams. The asymmetric funnel plot was done by Egger's asymmetric regression test and Begg's test. Data analysis was done using statistical software STATA (version 12). The significance level was considered as $P < 0.05$.

Results

We identified a total of 99 papers from all databases and initially excluded 29 duplicates. The flow diagram reporting trial selection is shown in Fig. 1. Briefly, by screening titles and abstracts, we excluded 70 references, leaving 29 for full-text review. Of these, 9 papers (30-38), involving 106 patients (51 male and 55 women) with type 2 diabetes together with 100 people as a control group (44 male and 56 women), were selected for inclusion.

Relationship between resistance exercise and blood glucose

The rate of blood glucose changes in studies which were meta-analyzed in present research varied from -11.73% (-19 mg / dl) to -37.18% (-82.1mg / dl). In total, the sum of reduction percentage of blood glucose in the present research underwent meta-analyzed was -22.11%. As the data in Figure 1 show a

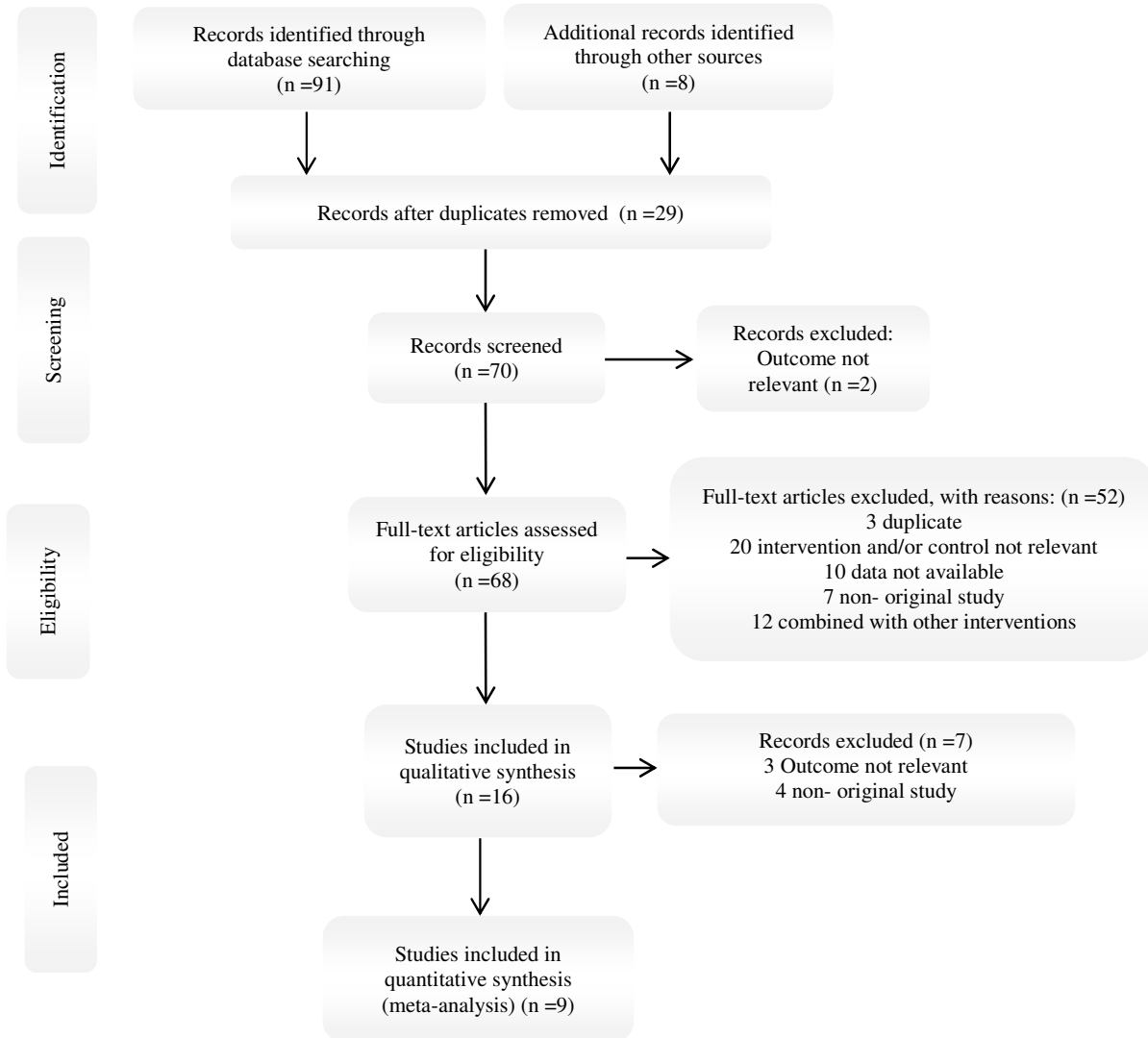


Figure 1. Diagram of study selection

statistically significant relationship is existed between resistance exercise and blood glucose in the conducted studies inside the Iran (SMD =-1.016; 95% CI= -1.367 to -0.756; $P=0.0001$). Regarding chi-square and I square indexes there was not any statistically significant heterogeneity among studies ($I^2=70.9\%$; $P=0.001$). Considering the homogeneity of studies, the fixed-effects model was used.

Relationship between resistance training and insulin

The rate of insulin changes in studies which were meta-analyzed in present research varied from -11% (-1 mU/l) to -59.93% (-10.051

mU/l). In total, the sum of reduction percentage of insulin in the present research underwent meta-analyzed was -26.98%. As the data in Figure 2 show a statistically significant relationship is existed between resistance exercise and insulin in the conducted studies inside the Iran (SMD =-0.609; 95% CI= -0.904 to -0.313; $P=0.0001$). Regarding the index chi-square and I square there was not any statistically significant heterogeneity among studies ($I^2=78.4\%$; $P=0.0001$). Considering the homogeneity of studies the fixed-effects model was used.

Relationship between resistance exercise and insulin resistance

The rate of insulin resistance changes in studies which were meta-analyzed in present research varied from -18.36% (-0.56) to -67.23% (-5.15). In total, the sum of reduction percentage of insulin resistance in the present research underwent meta-analyzed was -11.10%. As the data in Figure 4 show a statistically significant relationship is existed between resistance exercise and insulin resistance in the conducted studies inside the

Iran (SMD = -0.686; 95% CI = -1.006 to -0.366; $P=0.0001$). Regarding the index chi-square and I square there was not any statistically significant heterogeneity among studies ($I^2=90.3\%$; $P=0.0001$). Considering the homogeneity of studies the fixed-effects model was used.

The Forest plot figures 2-4 shows the relationship between resistance exercise and fasting blood glucose, insulin and insulin

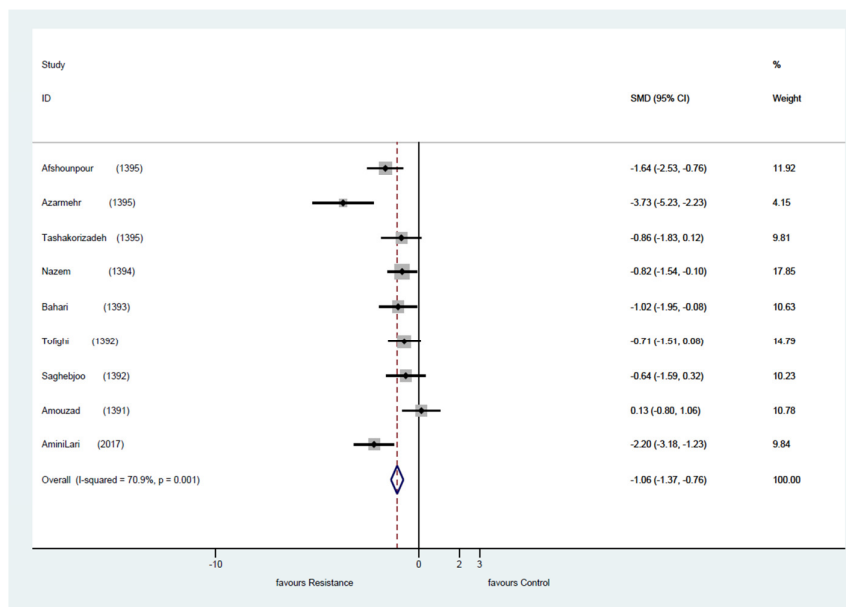


Figure 2. Forest plot of Relationship between Resistance training and blood Glucose

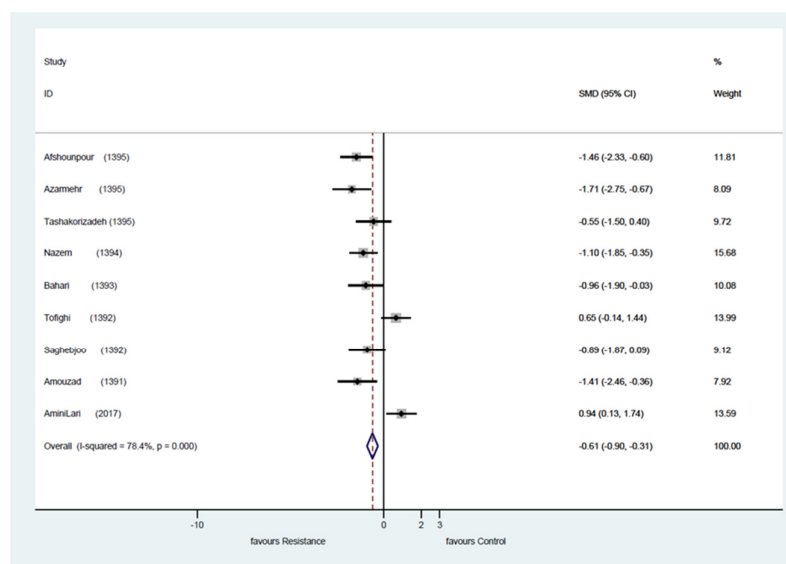


Figure 3. Forest plot of Relationship between Resistance training and Insulin.

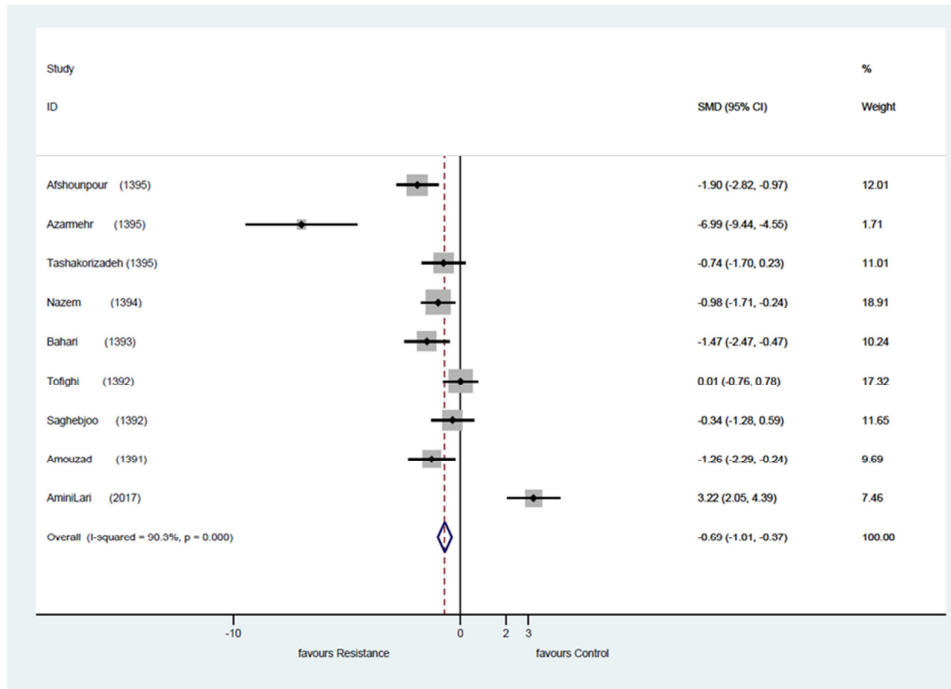


Figure 4. Forest plot of Relationship between Resistance training and Insulin resistance.

resistance at a 95% confidence interval based on fixed-effects model. The middle point of each segment shows the estimation of the outbreak rate and the segment length shows the 95% confidence distance in each study. The diamond sign shows the confidence distance for studies. Regarding that diamond cross zero line, it can be concluded that there is a significant relationship

between resistance exercise and blood glucose, insulin and insulin resistance.

Investigating Study publication bias

Begg's figure 5-7 have been plotted to identify publication bias and they show that publication bias have not affected the articles.

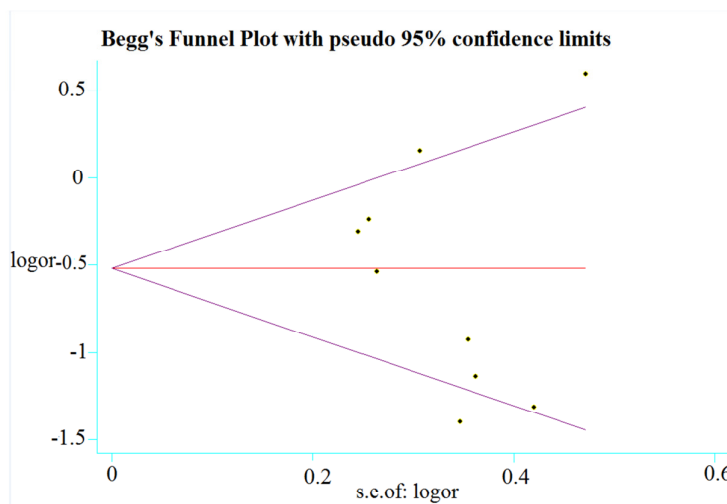


Figure 5. Begg's Funnel Plot for Relationship between Resistance training and Glucose (P=0.509).

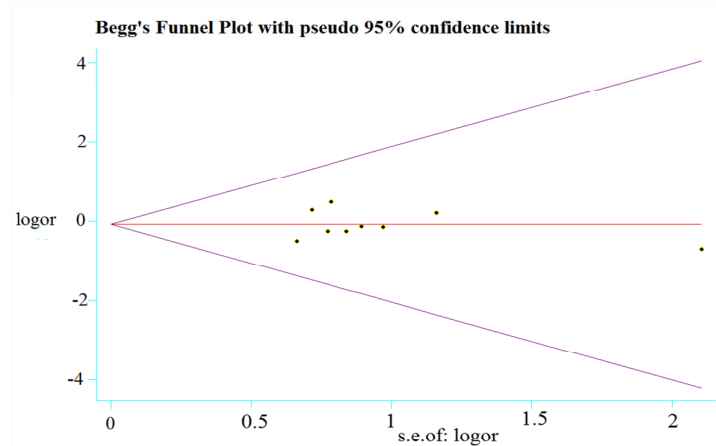


Figure 6. Begg's Funnel Plot for Relationship between Resistance training and Insulin ($P=0.534$).

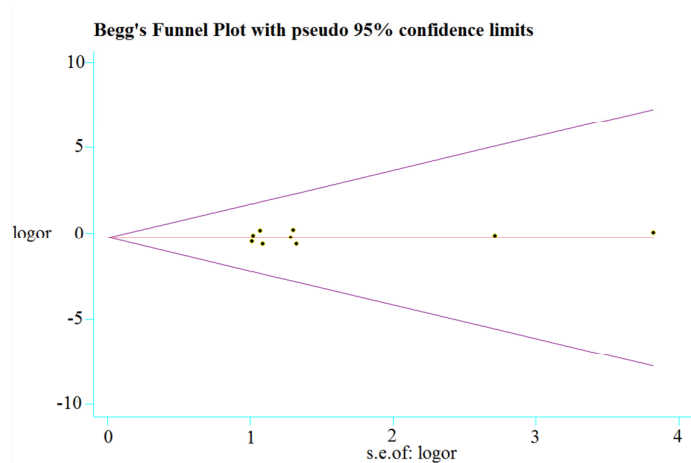


Figure 7. Begg's Funnel Plot for Relationship between Resistance training and Insulin resistance ($P=0.079$).

Discussion

In the present meta-analysis study we show that resistance exercise activities can lead to the decrease in blood glucose (-22.11%), insulin (-26.98%), and insulin resistance (-11.10%) in patients with type 2 diabetes. Resistance exercise increase insulin effect in skeletal muscle dramatically. The related mechanism involves inconsistencies such as increasing capillary density, increasing the amount of glucose-carrying proteins, especially GLUT4, and shifting to the types of insulin-sensitive myofibrils and possible changes in the composition of sarcolemma phospholipids, increasing glycolic and oxidative enzyme activity, and increasing glycogen activity synthesize (40). Exercise increases the activation of protein kinases with

adenosine monophosphate (AMP), which is induced by the increase in translocation of GLUT4 towards surface membranes. Also, AMP-activated protein kinase (AMPK) function increases the glucose transmission via the increase in the rate of GLUT4 on the cellular level in skeletal muscle resistance to the insulin and it mediated the GLUT4 expression effects (40). Indeed, positive changes in blood glucose are mainly caused by collective effects of several times reduction in the rate of blood glucose in each exercise (41). Aerobic exercise could changes the insulin effect on each muscle fibers without the increase in fibers, while resistance exercise preferably improve glucose absorption with the increase in the size of each fibers (42). In fact, repeated contraction of muscles during

exercises has an effect as insulin and transmits a high amount of glucose into the cell to produce energy. These repeated contractions increase the number of GLUT4 and membrane permeability to glucose (43). Also, it allows muscle fibers to have a lower glycolytic concentration for a relatively long period (44). As a consequence, the blood glucose and fructosamine reduce after a period of exercise (42). Muscle contraction has a pseudo-insulin role, and transfers a high amount of glucose into the cell to produce energy. Also, the exercise leading to mRNA rate reduction required to produce pro-insulin and glucokinase in the pancreas (45). So it seems that there are at least two cellular mechanisms to reduce the rate of insulin secretion. Firstly, pro-insulin mRNA reduction shows the insulin synthesis in the liver. Secondly, as the presence of glucokinase in the liver is essential for the pancreas beta cells sensitivities to the insulin; so the decreasing in the rate of glucokinase mRNA may lead to the decrease in the cells sensitivities to insulin and reduce its secretion (45). Also, another reason for the positive changes in glycemic control in patients with diabetes it can point that after bodily exercises the content of protein in insulin receptors and also the function of protein kinase B which plays a bias role in transmitting insulin signals is increased which can lead to blood glucose reduction (46). Also, it is possible that exercise induces changes in some of the cytokines, such as reduction in protein 4 retinol binding (RBP4) that participates in the regulating of insulin performance and carbohydrate metabolism as a adipokine and it has been characterized as one of the most effective factors in glucose

tolerance disorder and its consequence as diabetes. As it has been mentioned, exercise can reduce RBP4 followed by the glycemic control reduction in sensitivity to insulin in patients with diabetes (47). The mechanism of resistance training to reduce blood glucose is probably due to their same effects as insulin on the body and cause the remake of glycogen stores (glycogenesis) by muscle cells, which finally lead to normal blood glucose survival (48). Physiological and biomechanical responses to the resistance training than such responses in endurance exercises are different. It has been shown that resistance exercises just like endurance ones improve blood glucose level, increase insulin function in skeletal muscles, improve glucose tolerance and reduce HbA1c concentration. Since resistance exercise programs improve body sensitivity to insulin by skeletal muscles growth, this has a direct relationship with the increase in muscle mass and an adverse relationship with the increase in lipid mass. Several studies show that after resistance exercises, glucose extraction is increased due to the increase in net muscles mass (49).

Conclusions

Present study shows that resistance exercise training program in patients with type 2 diabetes has a significant effect on glycemic control. It is recommended that sport and medicine experts use resistance exercise as a non-pharmacological intervention for treatment of type 2 diabetes patients. Future long term studies focusing on patient-relevant outcomes are warranted.

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