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Effects of resistance training on insulin resistance and pancreatic-cells function in male patients with type 2 diabetes

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Abstract

Introduction: Physical activity improves the regulation of glucose homeostasis in both type 2 diabetes (T2D) patients and healthy individuals, but the effect on pancreatic β cell function is unknown. The aim of present study was to examine the effect of 8 weeks resistance training on pancreatic β-cells function and insulin resistance in male patients with T2D.

Material & Methods: Seventeen obese/overweight men (age: 53.1 ± 11.0 years and BMI: 27.0 ± 2.8 Kg/m^2 mean± SD) with T2D participated as the subject. The subjects were randomly assign to control group (n=8) or the resistance training group (n=9). Subjects executed six resistance exercises selected to stress the major muscle groups in the following order: chest press, shoulder press, latissimus pull

down, leg extension, leg curls and leg press. Resistance training consisted of 40-50 min of station weight training per day, 3 days a week, for 8 weeks. This training was performed in 6 stations and included 3 sets with 8-10 maximal repetitions at 70-80% of 1-RM in each station.

Results: The data indicated that fasting glucose (from 162.5 ± 27.8 to 116.7 ± 34.9 mg/dl; P=0.04), fasting insulin (from 6.6 ± 1.2 to 4.8 ± 1.6 IU/ml; P=0.03) and insulin resistance index (from 2.6 ± 0.7 to 1.4 ± 0.4; P=0.03) were decrease and pancreatic β-cells function (from 25.4 ± 7.8 to 42.6 ± 20.6; P=0.04) was increased significantly in the training group compare to the control group.

Conclusion: In summary, it seems that resistance training utilized in this study improves pancreatic β-cells function and insulin resistance in male patients with T2D.

Keywords: Resistance training, Diabetes, Hyperglycemia, Insulin resistance

1. Introduction

Type 2 diabetes (T2D) can be defined as a bihormonal metabolic disorder characterised by insufficient insulin secretion and abnormal glucagon secretion (1). According to International Diabetes Federation, estimated worldwide prevalence of diabetes was 382 million people in 2013 with a projection of 592 million people suffering from diabetes in 2030. It is well established that physical activity *per se* improves glucose homeostasis (2-4), a cornerstone of regulating overall glycaemic control among T2D patients.

T2D is sustained by insulin resistance and impaired insulin secretion. Impaired insulin secretion due to either β-cell dysfunction and/or β-cell loss is now recognized in the pathogenesis and progression of diabetes (5). Insulin resistance and dysfunction of the pancreatic β-cells characterize T2D and are already present before hyperglycaemia develops (6,7). The loss of β-cell mass and the progressive decline in β-cell function is an early feature of the natural history of diabetes and it

is detectable prior to diagnosis (5). The United Kingdom Prospective Diabetes Study (UKPDS) showed that β-cell function, as evaluated by the homeostatic model assessment (HOMA-B) index, was already decreased by 50% by the time of the diagnosis and that it continued to decline over the 6-year observation period, even with on-going hypoglycemic therapy (8). The relative increase of α-cells mass, another typical defect on Langerhans islets of diabetic subjects, may even precede β-cells loss, being already observed in normoglycaemic baboons with different degrees of obesity (9).

β-cell mass is influenced by a balance between proliferative and pro-apoptotic signals, which may be modulated by various growth factors, cytokines, and hormones, whose specific role in the rate of β-cell decline remains unclear. High levels of glucose and free fatty acids (gluco-and lipotoxicity), islet amyloid polypeptide deposition, and circulating inflammatory cytokines have been all implicated in β-cell apoptosis (9,10). At any rate, whenever it appears, impaired β-cell function leads to the progressive failure of islet cells to secrete sufficient amounts of insulin to overcome peripheral insulin resistance, ultimately resulting in failure to maintain normal glucose homeostasis over time. However, the rate of β-cell failure is unpredictable and not all persons with T2D will need insulin therapy to maintain their blood glucose levels (11).

Several factors may have a bearing on β-cell function, including healthy lifestyle – especially regular physical activity and exercise. Healthy life style provides clues to developing strategies to ameliorate the long-term management of T2D. Although previous studies indicated that insulin resistance (12,13) and β-cell function (12) were improved after aerobic training, the effect of resistance training on insulin resistance and β-cell function are not well known. Thus the aim of present study was to investigation of the effect of 8 weeks resistance training on pancreatic β-cells function and insulin resistance in male patients with T2D.

2. Materials and methods

Subjects

The study was designed to investigate 35–60-year-old participants as T2D is often diagnosed within this age range. Individuals with relatively

newly diagnosed T2D or with prediabetes (impaired fasting glucose and/or impaired glucose tolerance, based on the criteria by ADA) who could benefit from an exercise training intervention were recruited via announcements. The inclusion criteria were: male sex, age 35–60 years, BMI > 25 kg/m^2, no smoking and no exercise on regular basis at least 6 month before the intervention. A candidate was excluded if he had a condition which could potentially endanger their health during the study. The study was approved by the Islamic Azad University, Shiraz branch Ethics Committee. At the end, seventeen obese/overweight men (age: 53.1 $\pm$ 11.0 years and BMI: 27.0 $\pm$ 2.8 Kg/m^2 mean$\pm$ SD) with T2D participated in this study as the subject. The subjects were divided into training group (n=9) or control group (n=8).

Resistance training

Two familiarization sessions were designed to habituate subjects with the testing procedures and laboratory environment. The main aim of these sessions was to familiarize subjects with different resistance exercises using weight-training machines and also to familiarize them with performing the 1-RM test. During the familiarization sessions, it was ensured that all the subjects used the correct techniques for all exercises prior to taking part in the main test sessions. Subjects executed six resistance exercises selected to stress the major muscle groups in the following order: chest press, shoulder press, latissimus pull down, leg extension, leg curls and leg press. Resistance training consisted of 40-50 min of station weight training per day, 3 days a week, for 8 weeks. This training was performed in 6 stations and included 3 sets with 8-10 maximal repetitions at 70-80% of 1-RM in each station. General and specific warm-up were performed prior to each training session, as explained for the 1-RM determination, and each training session was followed by cool-down.

Anthropometric and body composition measurements

Height and body mass were measured, and body mass index (BMI) was calculated by dividing body mass (kg) by height (m^2). Waist circumference was determined by obtaining the minimum circumference (narrowest part of the torso, above the umbilicus) and the maximum hip

circumference while standing with their heels together. The waist to hip ratio (WHR) was calculated by dividing waist by hip circumference (cm). Body fat percentage was assessed by skinfold thickness protocol. Skinfold thickness was measured sequentially, in chest, abdominal, and thigh by the same investigator using a skinfold caliper (Harpenden, HSK-BI, British Indicators, West Sussex, UK) and a standard technique.

Blood samples and laboratory analysis

Fasting blood samples were collected at rest (before training) and after last session of training. All the subjects fasted at least for 12 hours and a fasting blood sample was obtained by venipuncture. Blood samples were kept in the temperature of –20°c. Glucose was determined by the oxidase method. Insulin was also determined by ELISA kit (Mercodia, Sweden). The intra and inter-assay coefficients of variation for glucose were <1.3% and a sensitivity of 1 mg/dl.

β-cell function was assessed with the HOMA-B model and insulin resistance was calculated using the HOMA-IR model (14,15).

HOMA-IR
= [Fasting Insulin (IU/ml) × Fasting Glucose (mmol/l)] ÷ 22.5

HOMA-B
= [(Fasting Insulin (IU/ml) × 360] ÷ [Fasting Glucose (mg/dl) – 63]

Statistical analysis

Results were expressed as the mean ± SD and distributions of all variables were assessed for normality. Paired-sample t-test, independent-sample t-test, wilcoxon and Mann-witney U teases were use for data analyzing. The level of significance in all statistical analyses was set at $P<0.05$. Data analysis was performed using SPSS software for windows (version 22, SPSS, Inc., Chicago, IL).

3. Results

Anthropometric and body composition parameters of the subjects are presented in Table 1. The data revealed body fat percent and WHR were decreased significantly in the resistance raining group in compare to the

control group (P<0.05). For body mass and BMI no significant changes were observed after the intervention.

Table 1. Anthropometric and metabolic characteristics (mean ± SD) of the subjects before and after training

	Control (mean±SD)		Resistance training (mean±SD)	
	Pretraining	Posttraining	Pretraining	Posttraining
Body mass (Kg)	77.2 ± 4.3	77.2 ± 4.1	81.6 ± 8.9	82.0 ± 9.4
BMI (Kg/m²)	26.7 ± 1.5	26.7 ± 1.6	27.3 ± 3.9	27.5 ± 3.9
Body fat (%)	28.1 ± 6.1	29.0 ± 5.4	30.8 ± 3.4	28.6 ± 2.6*†
WHR	0.944 ± 0.06	0.947 ± 0.06	0.977 ± 0.04	0.951 ± 0.05*†

*: P<0.05 for between-group differences.
†: P<0.05, pretraining vs. posttraining values.

Changes of fasting glucose concentration after 8 weeks resistance training are presented in the Figure 1. The date revealed that fasting glucose concentration was decreased after 8 weeks training (P<0.05), however no significant changes were observed in the control group.

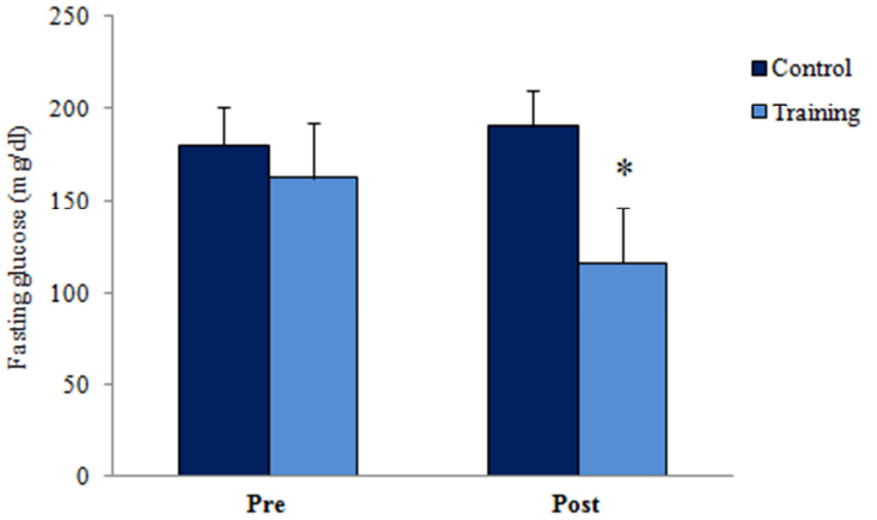

Figure 1. Changes of fasting glucose concentration after 8 weeks resistance training
* Significant differences (P<0.05)

Changes of fasting insulin level after 8 weeks resistance training are presented in the Figure 2. The date indicated that fasting insulin concentration was decreased after the intervention.

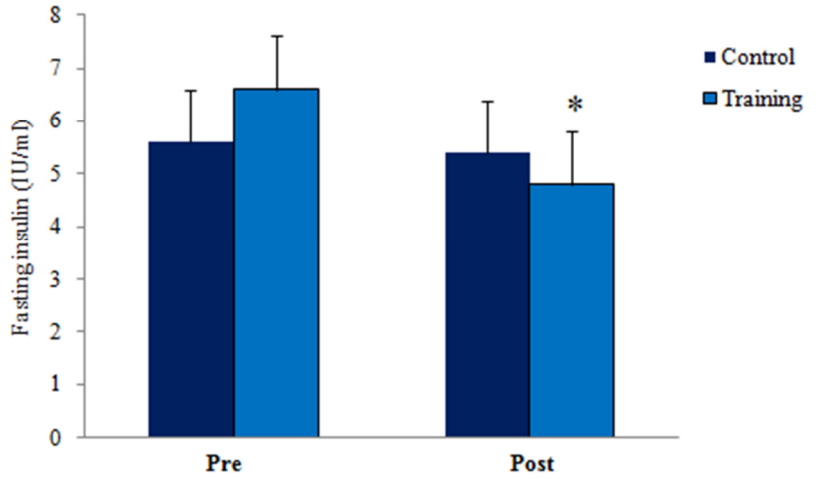

Figure 2. Changes of fasting insulin concentration after 8 weeks resistance training
* Significant differences (P<0.05)

Our data indicated that insulin resistance determined by HOMA-IR was decreased after 8 weeks resistance training (Figure 3); however no significant changes were observed in the control group.

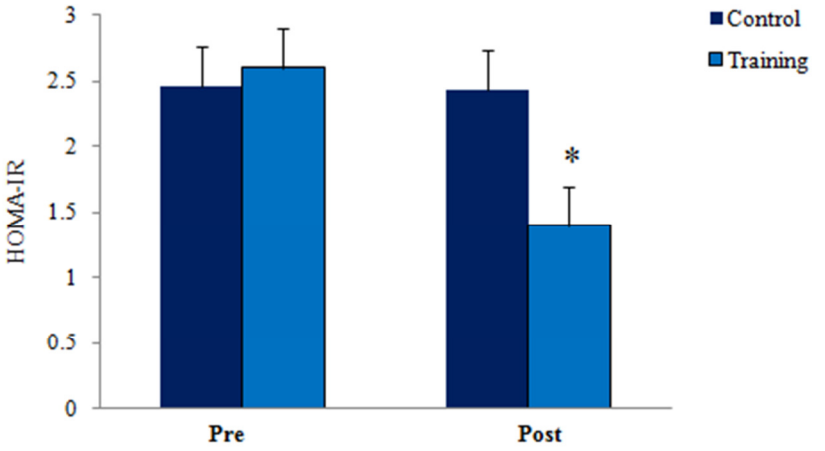

Figure 3. Changes of insulin resistance (HOMA-IR) after 8 weeks resistance training
* Significant differences (P<0.05)

Changes of pancreatic β-cells function determined by HOMA-B are presented in the Figure 4. The resistance training group significantly increased mean pancreatic β-cells function compared with baseline. No

other changes from baseline were noted in either group. Mean change scores for pancreatic β-cells function were significantly higher in the resistance training group compared with controls (P<0.05).

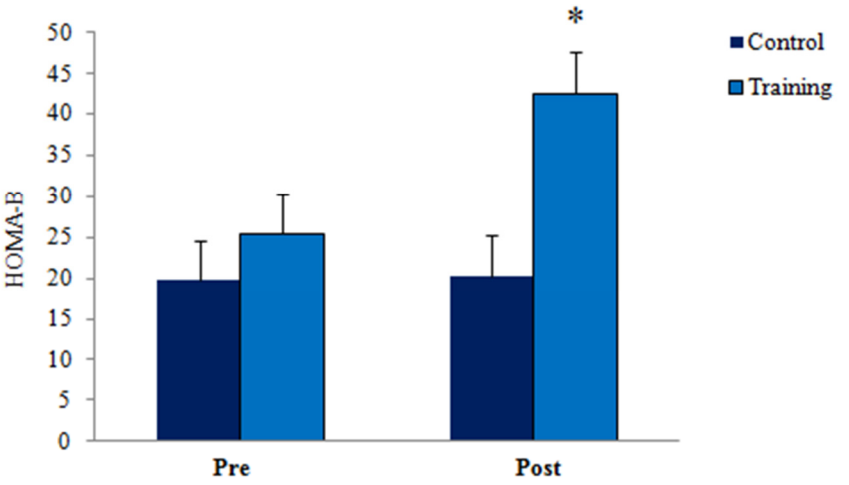

Figure 4. Changes of pancreatic β-cells function (HOMA-B) after 8 weeks resistance training
* Significant differences (P<0.05)

4. Discussion

T2D 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 (16). 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 T2D and it gradually expands the resistant to insulin and inefficiency of pancreas β-cells (17). Resistance exercises have been presented as the effective curative tools in many chronic diseases treatments like T2D (18,19). The aim of present study was to investigation of the effect of 8 weeks resistance training on pancreatic β-cells function and insulin resistance in male patients with T2D. Our data revealed that fasting glucose, fasting insulin and insulin resistance determined by HOMA-IR were decrease after 8 weeks resistance training. Previously, Krisan and colleagues (2004) established

that 12 weeks of resistance training effectively reversed diet-induced insulin resistance by increasing insulin-mediated glucose uptake in rodents (20). The improvements in glucose metabolism were associated with increases in GLUT4 protein concentrations as well as several key proteins involved in the insulin-signaling cascade. These findings were extended to humans by Holten et al. (2004), who investigated the effects of a 6 weeks resistance training program in adults with T2D. The training program consisted of 3–4 sets of single-leg lower-body exercises three times per week. The authors reported that leg glucose clearance in the trained leg was significantly increased compared with glucose clearance in nonexercising leg (euglycemic–hyperinsulinemic clamp with arteriofemoral venous catheterization). Further, the increased glucose clearance was not likely attributable solely to skeletal muscle hypertrophy, as changes in leg volume and muscle fiber size via biopsy were minimal. Thus, the investigators concluded that the mechanisms responsible for the improvements in insulin action included both up-regulation of components in the insulin-signaling cascade, such as protein concentrations of the insulin receptor, protein kinase B, and glycogen synthase, as well as the glucose transporter GLUT4 (21). On the other hand, resistance exercise increases 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 (22). 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 transmision 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 (22). 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 (23).

Aerobic exercise could changes the insulin effect on each muscle fibers without the increase in fibers, while resistance exercise preferably

improve glucose absorbtion with the increase in the size of each fibers (24). 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 (25). Also, it allows muscle fibers to have a lower glycogenic concentraction for a relatively long period (26). As a consequence, the blood glucose and fructosamine reduce after a period of exercise (24). 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 (27). 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 (27). Also, another reason for the positive changes in glycemic control in patients with diabete 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 (28). 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 (29). 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 (30). 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 concentraction. 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 (31). Collectively, these investigations support our finding that resistance training improves fasting glucose, fasting insulin and insulin resistance in male patients with T2D.

The results of the present study indicated that 8 weeks resistance training improves pancreatic β-cells function compare to the control group. Haffnet et al. (1996) noted that the β-cell malfunction is the primary cause of diabetes (32). Through regular exercise, less insulin can carry the same amount of glucose to muscles and the liver. Therefore, β-cells in the pancreas do not have to excessively secrete insulin, resulting in decreased HOMA β-cell indexes (32). The mechanisms behind the improved pancreatic β-cell function to increase insulin action could be multifaceted, including perhaps an improved coordinated feedback loop between liver (decreased hepatic gluconeogenesis), muscle (attenuated insulin resistance) and pancreas (slowly wakening of β islets to secrete insulin). However, given that T2D is a disease characterized by perturbations in several organs, anti-inflammatory cytokines secreted by both adipocytes (e.g. adiponectin) and myocytes (e.g. IL-6) could be involved in the improvement of pancreatic β-cell function (33).

5. Conclusion

Generally, present study shows that resistance exercise training program in patients with T2D has a significant effect on glycemic control, insulin rasistance and pancreatic β-cells function. It is recommended that sport and medicine experts use resistance exercise as a non- pharmacological intervention for treatment of T2D patients.

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Conflict of interests: There was no conflict of interest among authors.

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