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T –lymphocytes and cortisol response to resistance training in diabetics

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Diabetes mellitus is one of the largest global health emergencies of the 21th century. Each year more and more people live with this condition, which can result in life-changing complications. This study was designed to find out the effect of resistance training on T-lymphocytes, HbA1c% and cortisol hormone in type 2 diabetic patients. Sixty patients with type 2 diabetes. Their Age ranged from 40-50 years old, the duration diabetes mellitus was 4to7 years, Patients were of both sex. BMI between (25-34.9) kg/m^2, their HbA1c was not exceed 8%. The evaluation of serum cortisol level, T-lymphocytes (CD4) % and glycosylated hemoglobin (HbA1c) %was done before and after the study period for each patient. Patients were classified randomly into two groups, equal in number. (Control group, Group A) and (study group, Group B). Group (A) received their hypoglycemic drugs only. Study group (B) participated in 12 weeks resisted training program (3 sessions per week) in addition to oral hypoglycemic. Results showed a significant difference between (GA) comparing with the (GB) in post training values of serum cortisol level, T- lymphocytes (CD4) and Glycosylated hemoglobin (HbA1c) in favor of group (G B).So, it could be concluded that resistance training for 12 weeks in a diabetic patients caused significant increase in values of T-lymphocytes (CD4), and a significant decrease in serum cortisol level and glycosylated hemoglobin (HbA1c). So this type of exercise must be provided to diabetics to improve their quality of life.

Keywords: Diabetes, Resisted training, Cortisol, T-lymphocytes, Glycosylated haemoglobin

INTRODUCTION

The term "diabetes mellitus" describes a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin `secretion, insulin action, or both. The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organ (American Diabetes Association 2003).

Infectious diseases are common and serious complication of diabetes mellitus (DM) and hyperglycemia. The increase of infections in patients with DM is known to depend upon an immunosuppressive condition which is brought about by impaired innate immunity and acquired immunity. For instance, functions of neutrophils such as phagocyte, chemotaxis and cytokine-production are decreased in DM model mouse and hyperglycemia (Tanaka, 2008)

Regular exercise can lead to improvements in health-related factors including reduced glycosylated haemoglobin (HbA1c), delayed micro- and macrovascular complications, increased insulin sensitivity, improved glucose clearance and a predisposition to decreased mortality rate. While most of the above-mentioned health benefits have been attributed to aerobic exercise training, regular resistance exercise (RE), or 'strength training', can also promote better health of both type 2 diabetes (T2DM) and T1DM.(Turner D et al.,2013).

MATERIALS AND METHODS

This study is a controlled randomized study .Sixty patients (24male/36female) with type 2 diabetes were selected from The National Institute for diabetes and endocrinology, Ministry of health, while the exercise protocol was conducted at physical therapy unit in Cairo university pediatric hospital. They were divided into two groups equal in number, a written informed consent form is signed by each patient. The study protocol was approved by ethical committee of faculty of physical therapy, Cairo University.

Group (A): The control group, included 30 type 2 diabetic patients (12male/18female). They received their oral hypoglycemic drugs, only.

Group (B): The study group and included 30 type 2 diabetic patients(12male/18 female).They participated in 12 weeks resisted training program (3 sessions per week).

Inclusive criteria:

Participants with type 2 diabetes, of both sexes, duration of diabetes mellitus was 4to7 years. Their age between 40-50 years old. BMI between (25-34.9)kg/m^2. Glycosylated hemoglobin HbA1c not exceed 8%&patients under medical control with oral hypoglycemic drugs.

Exclusive criteria:

Participants with cardiovascular, orthopedic problems, neurological, musculoskeletal disorders, mental disorders, renal failure, myocardial infarction, pulmonary disorders, and Type 1 diabetes were excluded from this study.

Written informed consents were obtained from all patients who agreed to participate in the trial before study entry.

Methods: Each subject received detailed explanation of procedures of the program of training and measurement devices. The purpose of the training was explained for each subject**.**

Evaluation Procedures:

Blood sample for cortisol Level evaluation was collected for all subjects at 8:00 am (time of measurement is at fixed time). Total serum cortisol concentrations were measured with immunoassay method. Also Blood samples were collected for T- lymphocytes (CD4) percentage, and glycosylated hemoglobin percentage. Evaluation was taken for each patient before the study and after 12 weeks. Analysis of blood samples was done at laboratories of National Institute of Diabetes and Endocrinology.

Treatment procedure:

Warm up exercise: The resisted training program included a 5-min warm**-**up consisting of treadmill walking at low pace and stretching exercises.

Exercise Phase: The resisted exercise included exercises for the big muscles of upper limbs, lower limbs and abdominal muscles which consisted of single and multiple-joint resistance exercises including knee extensors. Knee flexors ,hip flexors , hip abductors ,hip extensors ,elbow flexors, elbow extensors , shoulder flexors ,and abdominal muscles using both free weights and sandbag weights ,using moderate work load for 30 minutes. The intensity of exercise program determined by Delorme method which was progressive in nature, with the number of sets, repetitions, and resistance used increased (Soliman et al., 2011) (table 1).

Table (1): Resisted exercise program (Soliman et al., 2011).

Weeks 1-4	Weeks5-8	Weeks 9-12
One set of 10-15 repetitions	Two sets of 8-12 repetitions	Three sets of 8-12 repetitions
60-75% of baseline 1 RM	More than 75-90% of baseline 1 RM	More than 90-97% of baseline 1 RM
1-2 min of rest between exercises	1-2 min of rest between exercises	1-2 min of rest between exercises

Cool down exercise: At the end of each session, there was a cool-down period consisting of treadmill walking at low pace and stretching for 5 min .

Table. (2): General characteristics of both groups

Variable	Mean ± SD in (GA)	Mean ± SD in (GB)	t-value	P-value	Significance
Age (yr)	45.30 ± 3.27	44.93 ± 3.32	0.431	0.668	Non
Weight (Kg)	85.13 ± 7.46	84.40 ± 7.12	0.389	0.698	Non
Height (cm)	165.76 ± 9.33	168.20 ± 10.02	- 0.973	0.335	Non
Body Mass Index (Kg/cm)	31.07± 2.72	29.9 ± 2.23	1.811	0.075	Non

P: probability, t: Student test, Non-significant: P > 0.05.

Table (3): Mean ±SD and p values of HbA1c pre and post-test in both groups.

HbA1c	Pre test	Post test	MD	% of change	t-value	p- value
	Mean± SD	Mean± SD				
Group A	7.37±0.73	7.39 ±0.95	-0.02	0.27	0.208	0.837
Group B	7.35 ±0.64	6.81±0.80	-0.54	7.34	3.136	0.004
MD	-0.02	-0.58				
t-value	0.094	2.545				
p- value	0.926	0.014				

*Significant level is set at P≤0.05 SD: standard deviation

MD: Mean difference p-value: probability value

Statistical analysis:

In this study, the descriptive statistics (the mean, the standard deviation, maximum, minimum and range) were calculated for all subjects in the study including HbA1c%CD4% and cortisol level variable.

Paired sample t-test was used to compare the difference between before and after treatment results of HbA1c%, CD4% and cortisol level variable. In the groups of the study, Unpaired t –test was used to compare the variables between groups. SPSS version 23 was used to compare the variables between groups. Significance level was set at p≤0.05.

RESULTS

General characteristics of both groups (The mean values of age, weight height and body mass index in both groups).

HbA1c:

1-Within groups:

As presented in table (3) within group's comparison the mean ± SD values of HbA1cin the "pre" and "post" tests were7.35±0.64 and 6.81 ±0.80respectively in the group (B). Paired t test revealed that there was significant reduction of HbA1cat post treatment in comparison to pre-treatment (t-value= 3.136, P-value =0.004). While, the mean ± SD values of HbA1cin the "pre" and "post" tests were 7.37 ±0.73 and 7.39±0.95 respectively in the group (A).Paired t test revealed that there was no significant difference of HbA1cat post treatment in comparison to pre-treatment (t-value= 0.208, P-value =0.837).

2- Between groups:

Considering the effect of the tested group (first independent variable) on HbA1c, unpaired t test revealed that the mean values of the "pre" test between both groups showed no significant differences with (t-value=0.094,P=0.926). As well as, unpaired t test revealed that there was significant difference of the mean values of the "post" test between both groups with (t-value=2.245, p=0.014) and this significant reduction in favour to group (B).

Table (4): Mean ±SD and p values of cortisol level pre and post-test in both groups.

Cortisol level	Pre test	Post test	MD	% of change	t-value	p- value
	Mean± SD	Mean± SD				
Group A	289.93±54.67	285.37 ±56.65	4.56	15.7	0.292	0.773
Group B	292.06±53.39	256.60±52.21	35.46	0.85	2.490	0.019
MD	2.13	-28.77				
t-value	-0.152	2.045				
p- value	0.879	0.045				

***Significant level is set at P ≤0.05** **SD: standard deviation**

MD: Mean difference **p-value: probability value**

Table (5): Mean ±SD and p values of CD4 pre and post-test in both groups.

CD4	Pre test	Post test	MD	% of change	t-value	p- value
	Mean± SD	**Mean± SD**				
Group A	**42.68±2.36**	**42.74 ±2.03**	**-0.06**	**0.14**	**-0.158**	**0.876**
Group B	**42.45±2.29**	**44.04±2.25**	**-1.59**	**3.74**	**-2.887**	**0.007**
MD	**-0.23**	**1.3**				
t-value	**0.393**	**-2.208**				
p- value	**0.696**	**0.031**				

***Significant level is set at P≤0.05** **SD: standard deviation**

MD: Mean difference **p-value: probability value**

Cortisol level:

1-Within groups:

As presented in table (4) within groups comparison the mean ± SD values of cortisol level in the "pre" and "post" tests were292.06±53.39 and 256.60 ±52.4 respectively in the group (B). Paired t test revealed that there was significant reduction of cortisol level at post treatment in comparison to pre-treatment (t-value= 2.490, P-value =0.019).While, the mean ± SD values of cortisol level in the "pre" and "post" tests were 289.93±54.67 and 285.37±56.65 respectively in the group (A).Paired t test revealed that there was no significant difference of cortisol level at post treatment in comparison to pre-treatment (t-value= 0.292, P-value =0.773).

2- Between groups:

Considering the effect of the tested group (first independent variable) on cortisol level, unpaired t test revealed that the mean values of the "pre" test between both groups showed no significant differences with (t-value= -0.152, P=0.879). As well as, unpaired t test revealed that there was significant difference of the mean values of the "post" test between both groups with (t-value=2.045, p=0.045) and this significant reduction in favour to group (B).

CD4:

1-Within groups:

As presented in table (5) within group's comparison the mean ± SD values of CD4in the "pre" and "post" tests were42.45±2.29 and 44.04 ±2.25respectively in the group (B). Paired t test revealed that there was significant increase inCD4% at post treatment in comparison to pre-treatment (t-value= -2.887, P-value =0.007). While, the mean ± SD values of CD4%in the "pre" and "post" tests were 42.68±2.36 and 42.74±2.03 respectively the group (A).Paired t test revealed that there was no significant difference of CD4%at post treatment in comparison to pre-treatment (t-value= -0.158, P-value =0.876).

2- Between groups:

Considering the effect of the tested group (first independent variable) on CD4%, unpaired t test revealed that the mean values of the "pre" test between both groups showed no significant differences with (t-value= 0.393, P=0.696). As well as, unpaired t test revealed that there was significant difference of the mean values of the "post" test between both groups with (t-value= -2.208, p=0.031) and this significant increase in favour to group (B).

Discussion

Diabetes mellitus is one of the largest global health emergencies of the 21St century. Each year more people live with this condition, which can result in life threatening complications. In addition to the 415 million adults who are estimated to currently have DM, there are 318 million adults with impaired glucose tolerance, which puts them at high risk of developing this disease in the future,(International Diabetes Federation, 2015).

Diabetes is a disease that affects the immune system and depletes body's defense system against infections. Regular exercise and metabolic control in diabetics can control blood sugar levels and increase defensive responses of the body,(Nikseresht et al., 2013).

In current study comparison of the mean values of post study total serum cortisol concentration in (GA) with the corresponding mean value in (GB) revealed a significant decrease in (GB) p**≤** 0.05.

Mohebbi., et al 2012agreed with our study. They investigated the effect of 8 weeks resistance training with different intensity on leukocyte count, IgG, cortisol and lactate concentration in untrained men. Twenty four untrained male were selected and randomly divided into three groups: high intensity (80%IRM)(n=8),low–intensity (50%IRM)(n=8) and control(n=8)groups. Resistance training program included (bench press, military curl, arm curl, lat pull down, leg press and leg extension), with three sets and 7-8 repetitions in high intensity group and 12-13repetitions in low intensity group. Blood sampling were collected in pretest , after 4th week and 8thWeek of training. Results showed that cortisol concentration in high intensity group increased significantly while cortisol concentration in low intensity group decreased significantly.

SoghraSujodi et al.,2013 also agreed with our results, they investigated the acute and chronic effects of 8 weeks of resistance training interval on the levels of cortisol, Dehydroepialdrosterone (DHEA), and the ratio of serum cortisol to DHEA in active young women. Fourteen subjects were examined in this study were randomly divided into exercise and control groups, blood samples were taken from all subjects at the beginning and end of 8 weeks, the results showed that cortisol significantly decreased (P<0.0 5).The results also showed that cortisol concentration in resistance training interval decreased significantly in comparison with cortisol concentration in control group after 8 weeks of resisted training.

The result of current study supported by Kraemer et al., 1999 they examined the adaptations of the endocrine system to heavy-resistance training in younger vs. older men. The authors studied two groups of men: (1) younger group (YG; *n* = 8; 29.8 ± 5.3 years), and (2) older group (OG; *n* = 9; 62 ± 3.2 years). The resistance training program consisted of a nonlinear, multiset, multi exercises program performed three times per week for 10 weeks. Resting blood samples were drawn 3 weeks before the start of training (−3) and at 0, 3, 6, and 10 weeks during training. The results showed that serum cortisol, has a significant lower concentration at 3 and 10 weeks than at 0 weeks for the older group.

Our results agreed with Ibañez J. et al., 2008, compared the effects of a twice-weekly whole-body supervised progressive resistance training program in older men with type 2 diabetes with those in healthy older men. Twenty sedentary older men participated in a 16-week progressive resistance training study. They were assigned either to a control group (*n*=11) or to a type 2 diabetes group (*n*=9). Lower as well as upper body maximal strength (one repetition maximum) and power testing and blood draws to determine basal hormone concentrations (total as well as free testosterone and cortisol) were conducted 4 weeks before training and then at Weeks 0 and 16. The training program consisted of intensities ranging from 50% to 80% of one repetition maximum, 5 to 15 repetitions per set, and three to four sets of each exercise. Baseline maximal muscle strength was not significantly different between groups. After training, the result showed that there was a significant decrease in the concentrations of total testosterone and cortisol between the control subjects and the patients with type 2 diabetes.

However our results contradicted with the results of Häkkinen et al. 2000 who examined the possible effects of weight training program (WTP) on basal hormone concentrations. Training sessions consisted of three to four sets of seven exercises for major muscle groups. Training load progressed as follows: months 1–3: 50 to 70 % of 1-RM and month 4: two phases with 50 to 60 % and 70 to 80 % of 1-RM. During months 5 and 6, subjects performed 8–12 repetitions of 50 to 60 % of 1-RM with a fast concentric for explosive strength. Strength and serum cortisol was measured at baseline 2, 4, and 6 months. Following the training program, no changes were observed in cortisol concentrations during the training or at the end of training among groups.

Resistance training (RT) has been recently noted to improve glycemic control maintain bone mineral density, increasing muscle strength, and preventing osteoporosis. Resistance training may be the first choice for patients with diabetes who are unable to elicit substantial energy expenditure from aerobic training. Improving glycemic control is essential for preventing various long-term diabetes-related complications (e.g., blindness, amputation, dialysis, cardiovascular disease) that affect quality of life. (Hajime Ishiguro et al, 2016).

In current study comparison of the mean values ofHbA1cpercentage post study in (GA) with the corresponding mean value in (GB) revealed a significance decrease in (GB) p**≤** 0.05. Baldi and Snowling, 2003, agreed with the results of the current study, they mentioned that RT is an effective form of exercise training which can improve glycaemic control and lower fasting insulin levels in obese type 2 diabetics. Eighteen subjects were randomly assigned to a 10-week RT program, or a non-training control group (C). Glycosylated haemoglobin (HbA1c), fasting glucose and insulin, glucose and insulin 120 minutes (2h) after a 75 g oral glucose load, body composition and muscular strength and endurance were measured before and after the 10-week experimental period. The results showed that, in the RT group fasting glucose and insulin decreased with training (p < 0.05) and decreases in HbA1c approached significance (p = 0.057).

The results of the current study was also supported by Eriksson J et al.,1997 who investigated the effect of circuit resistance training on long-term glycaemic control (HbA1c) and the potential association between muscle size and glycaemic control in NIDDM subjects. Eight NIDDM subjects participated in a 3 months individualized progressive resistance training program (moderate intensity, high-volume) twice a week with measurements of HbA1c, lipids, blood pressure, VO2 max and thigh muscle cross-sectional area. The results showed that there was a significant improvement in HbA1c (8.8% - 8.2%; p < 0.05) after 3 months progressive resistance training program.

The results of current study was also supported by Salameh Bweir, et al.,2009 who investigated the effects of 10 weeks of resistance or treadmill exercises on glycemic indices levels prior to and immediately following exercise in adults with type 2 diabetes. Twenty inactive subjects (mean age 53.5 years) with type 2 diabetes enrolled in the study. Baseline HbA1c, blood glucose levels, heart rate, and blood pressure were measured for each subject prior to the initiation of the exercise program. Subsequently, subjects were matched to age, waist circumference and sex and assigned to either resistance or treadmill exercise groups, which met 3 times per week for 10 weeks. The results showed that there were significant improvements in the mean HbA1c reading pre and post training in both groups (p < 0.001). However, the greater reduction was noted in the resistance exercise group, and at 10 weeks their HbA1c levels were significantly lower than the group that received treadmill exercises (p < 0.006).

In another study by Abd El-Kader SM et al., 2011 subjects were divided into two equal groups: the first group (A) received aerobic exercise training. The second group (B) received resisted exercise training three times a week for three months in order to compare the effect of aerobic and resisted exercise intensity on TNF-α, IL-6, HOMA-IR and HbA1c in obese type 2 diabetic patients. The mean values of TNF-α, IL-6, HOMA-IR and HbA1c were significantly decreased in both groups.

In agreement with the results of current study Dunstan DW et al., 2002 examined the effect of high-intensity progressive resistance training combined with moderate weight loss on glycemic control and body composition in older patients with type 2 diabetes. Sedentary, overweight men and women with type 2 diabetes, aged 60–80 years (*n* = 36), were randomized to high-intensity progressive resistance training plus moderate weight loss (RT & WL group) or moderate weight loss plus a control program (WL group). Clinical and laboratory measurements were assessed at 0, 3, and 6 months.HbA_{1c} fell significantly more in RT & WL than WL at 3 months (0.6 ± 0.7 vs. 0.07 ± 0.8%, *P*< 0.05) and 6 months (1.2 ± 1.0 vs. 0.4 ± 0.8%, *P*< 0.05).

In the last decade, there has been a remarkable increase in the number of descriptive studies on exercise and the immune system. The available evidence shows that exercise has modulatory effects on immunocyte dynamics and possibly on immune function. These effects are mediated by diverse factors including exercise-induced release of proinflammatory cytokines, classical stress hormones, and hemodynamic effects leading to cell redistribution (Rodrigo et al., 2012).

In current study comparison of the mean values ofCD4percentage post study in (GA) with the corresponding mean value in (GB) revealed a significance increase in (GB) p**≤** 0.05.

The results of current study was supported by Miles MP.et al., 2002 Who investigated the effect of intense resistance training of 6 months duration influenced resting immune parameters. Previously untrained women underwent one of four training programs or were non-training controls (control, n=7). The resistance-training groups trained for total body power (TP, n=16), total body hypertrophy (TH, n=18), upper body power (UP, n=15) or upper body hypertrophy (UH, n=15). Immune parameters were measured from a fasting morning blood draw. In 0,3 and 6 months Lymphocyte subsets [CD4+ T cells, CD8+ T cells, natural killer cells (NK), and B cells], and mitogen-stimulated proliferation were measured. The concentration of NK cells increased (P<0.001) after 3 months of training for the resistance-training groups but not the control group. This increase was not present after 6 months of training, thus it was a transient change. Lymphocyte proliferation responses were similar across time for the resistance-trained and control groups for all stimulation conditions. Thus, resistance training induces a transient increase in NK cells but has little effect on lymphocyte trafficking or proliferation.

Miles MP.,et al 2003on their investigation to determine whether the immune response to resistance exercise was associated with changes in workload or anaerobic exercise intensity. Previously untrained women underwent 6 months of resistance training for lower and upper body. Lymphocyte subsets [T (CD3+), CD4+, CD8+, NK and B], functional markers (CD45RA+ and CD45RO+), and mitogen and superantigen (staphylococcus a. cowans) stimulated proliferation were measured from blood samples collected pre- and post-exercise With respect to anaerobic intensity, exercise-induced increases in NK, CD4+, CD8+ and B lymphocyte concentrations which agreed with results of current study.

Shimizu K.,et al., 2008 Also agreed with the current study .They investigated the effect of moderate exercise training on T-helper cell subpopulations in elderly people**.** Subjects in exercise group participated in exercise sessions 5-days a week for 6 months. (endurance training and resisted training) Meanwhile, subjects in control group maintained their normal physical activity levels during the study period. Blood samples were collected before and after the training period. Samples were measured for the number of leukocytes and lymphocytes, as well as for CD3+, CD4+, CD28+CD4+, IFN-gamma+CD4+, IL-4+CD4+ cells. The number of leukocytes, lymphocytes, and CD3+ cells did not change after 6 months in both exercise and control. The number of CD4+ and CD28+CD4+ cells significantly increased after the training in exercise (P < 0.05), while control did not show significant changes. The results showed that exercise training might upregulate monocyte and T-cell-mediated immunity in elderly people.

However RasoV et al, 2007 disagreed with our study, they investigated the effect of a 12-month moderate resistance training program on phenotypic and functional immunological parameters of previously sedentary, clinically healthy, elderly women. Resistance training program consisted of three sets of 12 repetitions at 54.9 +/- 2.4% 1RM for five different exercises performed three times per week during 12 months. Natural killer cell cytotoxic activity (NKCA), lymphoproliferative response to the mitogen phytohemaglutinin (PHA), and quantification of the lymphocytes (CD3, CD3CD19, CD56) and subpopulations (CD4, CD8, CD56, CD56) as well as cellular expression molecules (CD25, CD28, CD45RA, CD45RO, CD69, CD95, HLA-DR) were determined by immunological assays. There were no statistically significant differences between the groups for quantitative (CD3, CD3CD19, CD56, CD4, CD8, CD45RA, CD45RO, CD56, CD56, CD95, CD28, CD25, CD69, HLA-DR) and functional immunological parameters (natural killer cell cytotoxic activity and lymphoproliferative response).

CONCLUSION

We found that the application of resisted training for 12 weeks in a diabetic patients indicated a significant decrease in values of serum cortisol level, and glycosylated haemoglobin (HbA1c) with increase in T-lymphocytes (CD4) value, So this type of exercise can be provided to diabetics to improve their immunity and decrease their cortisol level and glycosylated haemoglobin (HbA1c) percentage when may improve their quality of life.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors contributed equally in all parts of this study. All authors read and approved the final version.

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