Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Scholars Research Library

Annals of Biological Research, 2012, 3 (2):930-937
(http://scholarsresearchlibrary.com/archive.html)

Annals of Biological Research
Scholars Research Library
ISSN 0976-1233
CODEN (USA): ABRNBW

The Effect of 6 weeks resistance training on serum levels of IGF-1 and IFN-γ in type I diabetic male rats

Fateme Zolfaghari[1*], Maryam Vatandost[1], Hamid Agha-alinejad[2], Maghsood Peeri[1]

[1]Department of Physical Education & Sport Science, Faculty of Humanities, Central Tehran Branch, Islamic Azad University, Tehran, Iran
[2]Department of Physical Education & Sport Science, Faculty of Humanities, Tarbiat Modares University, Tehran, Iran

---

ABSTRACT

Diabetes mellitus (DM) and chronic inflammation are strongly related to increased cardiovascular risk. This study aims to investigate the influence of physical training on the inflammatory markers of diabetic rats. Adult male Wistar rats were distributed into Sedentary Control (SC), Trained Control (TC), Sedentary Diabetic (SD) and Trained Diabetic (TD) groups were used. Diabetes was induced by Stroptozotosin (55 mg/bw-i.v.). Training protocol consisted of resistance training (elevate upward weights), at 32 +/- 1 degrees C, one hour/day, five days/week, supporting an overload equivalent to 5% of the body weight, during four weeks. At the end of the experiment the rats were sacrificed by decapitation and blood samples were collected for glucose, IFN-γ and IGF-1 determination. The results were analyzed by one way at a significance level of 5%. Diabetes reduced blood insulin, HDL and increased blood glucose, IFN-γ and IGF-1.TG and LDL count. Physical training restored glycemia and inflammatory markers count in diabetic rats. In summary, physical training was able to improve metabolic and immunological aspects in the experimental diabetic rats.

Key Words: Physical training, inflammatory markers, diabetes mellitus, Rats.

INTRODUCTION

Many chronic diseases are now in pandemic proportions and increasingly a major cause of morbidity and mortality worldwide. Diabetes mellitus plays a starring role in this problem (1,2) with diabetic complications being a very important public health issue.

Recently, the effect of physical activity on immune function has been studied intenselyin diabetics patient. This is an important area of study because exercise may modulate the immune system's ability to monitor and protect the individual from disease and to repair damage. In most of these studies, aerobic exercise (AEX) and aerobic conditioning (ACO) have been the independent variables. Consequently, the functional immune response to ACO seems relatively clear. However, the immune response to resistance exercise (REX) is not as clear because few studies have been published. The immune response to REX may be different than that to AEX because of the different physiological demands of these 2 types of exercise. Resistance conditioning (RCO) does not have a significant effect on heart rate, blood pressure, cardiac output, stroke volume, vascular resistance, or the arteriovenous oxygen saturation difference during submaximal treadmill exercise (3,4).

Certainly the role of IFN-γ in the development of diabetes is supported by several studies the literature.This evidence can be summarized as folliws:1) Addition of IFN-γ , alone or in combination with other cytokines like TNFα/β or IL-1 , to pancreatic islets in vitro inhibited insulin secretion and resulted in destruction of the islet-β-cells has showed that pancreatic expression of this important type 1 cytokine is capable of inducing insulitis and diabetes in nondiabetes-prone mice.3)Deletion of IFN-γ by IFN-γ gene-targeted-disruption (GKO) in the NOD mouse showed that the absence of IFN-γ delays the destructionprocess of the β-cells and the development of diabetes .and mutation of the gene encoding the IFN-γ receptorwas reported to markedly inhibit insulitis and completely prevent diabetes development.also , deletion of IFN-γ by administration of anti IFN-γ monoclonal antibody in both NOD mice and BB rats,or by administration of soluble IFN-γ receptor , led to protection against diabetes.It is important to note that the association of IFN-γ with disease progression is not necessarily a systemic phenomenon but localized to the insulitis lesion.

Steensberg (2001) the found that after running for 2.5 hours with the 75% of VO2max by 9 men endurance runner the percent of the CD4† to CD8† reduce the production of the IFN-γ.

The type 1 cytokine IFN-γ is a key cytokine in the development of autoimmune diabetes ,and any treatment or intervention that leads to protection against the development of disease is associated with down regulation of IFN-γ .when IFN-γ is absent or down regulated ,the β-cells are spared from the destruction by the effector molecules (perforin, granzyme B ,and IFN-γ). However, the protection against β-cell destruction is primarily due to the absence of IFN-γ.

However, there are few data about of the impact resistance exercise on inflammatory markers function and inflammation in type 1 diabetes, especially in type 1 diabetic patients.

The aim of this study was thus to investigate whether a 6-weeks supervised resistance exercise program could suppress the inflammatory cascade and trigger anti inflammatory mediators in male rats with type 1 DM.

MATERIALS AND METHODS

Male Wistar rats were used in the experiments (180-210 g; 40-day-old). They were kept at 25°C with a 12/12 light/dark cycle, and fed with Purina rat food and water *ad libitum*. All experiments with the animals were performed in accordance with the specific Brazilian resolutions of the Bioethics of Experiments with animals (law N° 6.638 of May 8th 1979; Decree N° 24.645 of July 10, 1934, Brazilian College of Animal Experimentation).

Diabetes induction

Diabetes was induced by an intravenous injection (55 mg/kg b.w.) of Stroptozotosin. After two days, blood samples were obtained with animals in the fed state to determine the plasma glucose concentration. Rats which were not diabetic (<14,7 mmol/L) or too severely diabetic (>35,5 mmol/L) were eliminated from the study.

Training protocol

Climbing of a ladder with 2 cm grid ladder inclined with 26 steps at 85 degrees with weights attached to their tails was used as a resistance exercise. Rats were familiarized with the exercise for three days. Three days after familiarization, the resistance training was begun using cylinders containing weights that were attached to the base of tail with foam tape (3M Conan), a Velcro strap and a hook. Briefly, the cylinders were fastened to the tail by wrapping the upper portion of the tail (2-3 cm from the proximal end) with Velcro on top of foam tape. Then, the appropriate weights were inserted into the cylinders. The rats were positioned at the bottom of the climbing apparatus and motivated to climb the ladder by grooming action to the tail. The initial weight attached was 30% of their body weight for diabetic group and 50% of their body weight for control group and increased gradually throughout the 5 weeks of training period. The resistance training consisted of five sets of 4 repetitions with a 3 min rest interval between the reps and 30 to 60 seconds between the sets for 5 weeks. When the rats reached the top of the ladder, they were allowed to recover in the resting area. This procedure repeated until either the rat finished all three set of training or failed to climb the entire length of the ladder. Electrical shock (0.2-3m Amp) was used to motivate the rat to climb when necessary.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 16, was used for statistical analysis. All data are presented as mean ± SEM. Before statistical analysis, all variables were checked for normality and homogeneity of variance by using the Kolmogorov-Smirnoff and Levene tests, respectively. The data obtained were tested by ANOVA followed by Tukey's post-hoc multiple comparison test. $P<0.05$ was considered statistically significant.

RESULTS

Although the mean of healthy control group is less than other groups significantly ($P>0.05$), there is no significant difference among averages in evaluating gamma interferon concentration ($P>0.05$). There was a significant difference between the means of diabetic control group and healthy control group ($P=0.001$) in evaluating growth factor of 1-pseudoinsulin. Also, there is a significant difference among the means of exercised diabetic and healthy control ($P=0.002$) and

exercised healthy groups (P=0.000). Both the means of diabetic control group and diabetic exercised group is less than the mean of healthy control group and exercised healthy group. There is a significant difference among the means of diabetic control group with healthy control group (P=0.000) and healthy exercised group (P=0.000) about glucose levels. Also, there is a significant difference among the means of exercised diabetic group with healthy control group (P=0.000) and healthy exercised group (P=0.000), while there is no difference among diabetic groups (P=0.05).

Table 1: comparison of Weight, IGF-1, IFN-γ and Glucose levels in groups

Groups / Variables	Normal control	Healthy exercised	Diabetes control	Diabetes exercised
Weight before diabetes	266.9	260.38	262.5	261.75
Final weight	320.3	317.38	232.5	248
IGF-1 (ng/ml)	549.06±200.99	636.16±193.72	91.91±52.99*	110.91±48.23*
IFN-γ (pg/ml)	17.62±1.45	21.24±7.05	22.74±3.62	21.45±6.22
Glucose	4.52 ±0.124	4.34 ±0.12	30.37 ±1.21	27.76± 1.41

Asterisks in the superscript indicate significant difference at the level of 0.05.

DISCUSSION

In the present study it was apparent that the weight of healthy control group and healthy exercised group increased following 6 weeks of endurance exercise while the weight of diabetic control group and exercised diabetic decreased significantly. Glucose levels of healthy exercised group decreased significantly compared with healthy group. Glucose levels increased in diabetic control group compared with healthy group and in exercised diabetic group there was a significant decrease compared with diabetic control group. It has been reported that 16 weeks of heavy increasing endurance exercise in diabetic aged people leads to improve glycemic condition (11). In another report it was reported that 6 months increasing endurance exercise as well as weight loss in 2-type diabetic aged people causes to semi-improvement of lipidemic and glycemic condition (14). In a study conducted by Ericsson et al. in 1997 it was proved that circular exercises have a role in controlling blood glucose (23) also, increased muscular mass following endurance exercises has a role in diabetes treatment and decreasing diabetes side-effects (10, 20). Kastanda et al. in 2002 reported that 16 weeks of heavy increasing endurance exercise in diabetic aged people leads to improve glycemic condition (11).

IFN-γ levels showed no significant difference in our exercise program although it has decreased in exercised diabetics compared with diabetic control group but the decreased was not significant. Strowsky et al in 1999 evaluated the effect of running for 3:26 hours on IFN-γ in 10 men with average of 27years old. The results of the study showed the increase of IFN-γ immediately post-exercise hours (15). The results of another study conducted by Gannon et al. in 1997 on 6 amateur cyclists showed that IFN-γ was lower than the threshold level after 250 km cycling for 404 minutes (16). Also, Lakester et al in 2004 in a study similar to that conducted previously reported that the rate of IFN-γ decreased following heavy activity and this phenomenon was attributed increase infection among athletics.

Some studies reported no changes in post-sport production of IFN-γ (18); also, post-sport increase (18, 19) and decrease (20) of IFN-γ has been reported. It was reported in another study that in 7 men the percentage of IFN-γ producing CD8 cells was decreased significantly following 1.5 km running in 75% VO2max of the course (16)m in another study it was reported that 8 weeks endurance exercises can affect significantly on serum IFN-γ , IL-6, and cortisole such that decreases their concentration (31). Avatta has introduced gamma interferon gene as a genetic sign for type-1 diabetes. Probably, TT cytokaein gamma interferon can prohibit the disease (22). No changes in IFN-γ concentration following heavy exercise for 68 minutes have been reported (19). In a study conducted by Gannon et al. in 1997 on 6 armatures, concentration of IFN-γ was lower than the primary concentration following cycling (11). IFN-γ is a immune-modulator cytokaien that effects on immunity system function also its secretion increases in inflammatory cases (25).

It has been demonstrated that 8 weeks of aerobic and endurance exercises lead to decrease the production of gamma interferon and plasma IL-17 in people suffering multisclerosis disease. The researchers suggested that compound exercises have anti-inflammatory effects (23). In contrast with the present study, it was shown in another study those 6 weeks exercises (2.5 hours in a week) decreased the production of gamma interferon by monocytes in people exposed to heart ischemic. Golhummer et al. in 2005 demonstrated that 12 weeks of aerobic exercises decreases pre-inflammatory cytokaeins like gamma interferon (22). In consistent with findings of the present study, Kordrow et al. in 2009 showed that 14 weeks running on treadmill doesn't change the release of gamma interferon and IL-1β from microfages in fat rats (18).

In the present study, IGF-1 levels has been decreased in diabetic control group rats compared with healthy control group which is a normal task since, IGF-1 levels decrease highly in diabetic patients while the endurance exercise conducted in the present study, increased slightly the IGF-1 levels in diabetic patients which is maybe due to intensity and duration of our exercise protocol.

IGF-1 levels in diabetic patients decreases (30). IGF-1 concentration decrease was reported in 387 diabetic patients (28). Decrease of insulin portal level and excessive secretion of IGFBD-1 by liver are the main reasons of IGF-1 decrease in diabetes which causes to increase growth hormone (26). Diabetics suffer definitely more than other people from tissue injuries. Since, tissue rehabilitation needs local increasing of IGF-1 in injured region, decreasing in the rate of IGF-1 can prohibit the forming of relevant reactions for tissue rehabilitation and provide the conditions for primary injuries (32). Most studies didn't show any change in IGF-1 during or immediately following heavy endurance exercise while, some studies have shown sever increase during and following endurance exercise. Lack of changes in IGF-1 is attributed to delayed secretion of IGF-1 (3-9 hours later) following stimulated synthesis of mRNA by GH such that the maximum rate may not be obtained 16-28 hours post-stimulation of GH release (28). It seems that the increase of IGF-1 following a heavy endurance exercise may delay synthesis and stimulated secretion by GH from liver (23).

Relaxation concentrations of IGF-1 increase during normal endurance exercises along with carbohydrate and/or protein supplementary. Also, long term studies on women have demonstrated increase in relaxation IGF-1 especially during intensive exercises (32).

Therefore, it seems that the increase of IGF-1 following a heavy endurance exercise may delay synthesis and stimulated secretion by GH from liver (26). These kinds of paracrinic effects have been suggested by other studies and figured as important factors in muscular hypertrophy. Researchers demonstrated that one stage of heavy endurance exercise doesn't affect IGF-1 but affects on a channel in which IGF-1 separates from bonding proteins .

Furthermore, decrease of IGF-1 (app.11%) during hyperexercise period has been reported but when the period lowers, IGF-1 returns to its baseline levels. So, it seems that the intensity and volume of exercises are important for chronic compatibilities of IGF-1 (23). There are equal evidences suggest that circulating IGF-1 levels increase by both chronic endurance or resistance and the increase is proportional to VO2max and body activity. So, body reaction occurs during 2 weeks exercise in which the baseline level of IGF-1 increases more than 37%. It has been reported that the age-related decrease demonstrates the decrease in body fitness. Although this issue has been challenged in other studies, it isn't clear whether the IGF-1 is responsible for changes in muscular form and structure which occur with chronic exercises or not. In the studies conducted on animals the 200% increase of IGF-1 immunity activity in rats' leg muscles following 4 days of heavy endurance activity which leads to muscular hypertrophy .

It has been demonstrated that heavy exercise causes to increase muscular and circulatory IGF-1 in diabetic rats. The diabetes causes to less increase of IGF-1 in response to one exercise session in children suffered by type-1 diabetes compared with healthy control group (24). Conforming to our findings, dolly et al. in 2005 demonstrated that 6 months of endurance exercise along with caloric limitation program in aged people suffered by type-2 diabetes causes no changes in relaxing concentration of IGF-1 (30). It has been reported that 16 weeks of endurance exercise made no IGF-1 changes in 343 type-2 diabetic patients (9). Also, decrease in IGF-1 concentration has been reported following exercises in diabetic people. It has been observed that 2 weeks of regulate body activity in adolescents suffered by type-1 diabetes causes to decrease serum IGF-1 and IGFBP-3 (25) while, long term studies have reported IGF-1 improvement. So, it seems that the volume and intensity of exercises are important for chronic compatibilities of IGF-1. Therefore, no changes in IGF-1 concentration in the present study can be due to the shortness of the study time (5 weeks) or due to changes in bonding proteins levels. Generally, it can be said that 5 weeks of endurance exercises is not a sufficient time for observing the improvement of type-1 diabetes in mentioned factors. The present study was conducted due to important role of semi-insulin growth factor in endurance exercise and diabetes as well as due to important role of gamma interferon in diabetes. It can be concluded that 6 weeks endurance exercise couldn't make significant changes in IGF-1 and IFN-γ and glucose and the changes were not significant. But small changes can be important clinically in improving patient's recovery. 6 weeks of endurance exercise increased the IGF-1 levels although the increase was not significant. The IFN-γ levels decreased by our exercising protocol but it were not significant. Serum glucose levels in exercised diabetic group were lower compared with diabetic control

group which could be very important clinically although that was not significant; but these changes can be a positive sign of endurance exercises in improving type-1 diabetes.

The present study suggests that the mentioned factors can be conducted in longer times and different intensities by future studies since an endurance exercise with high intensity maybe have some roles in significant changes of mentioned factors.

REFERENCES

[1] Doustar Y, Salehi I ,Mohamadi M , Mohajeri D, Hashemi M, *Medical Science Journal of Islamic University*, Tehran medical unit **2007**;Under press.
[2] Yousef Doustar , Mostafa Mohammadi, Darush Mohajeri and Mehrdad Hashemi, *Medical Science Journal of Islamic Azad University*, Tehran Medical Branch .
[3] Iraj Salehi ,Mustafa Mohammadi, Amir Ahsadi Fakhr. *Scientific Journal of Hamadan University of Medical Sciences & health Services* **2009**, 16(2).
[4] Boulton M , Gregor Z , Mcleod D , Charteris D , Jarvisevans J , Moriarty P , et al. *Br Ophthalmol* **1997**:
[5] Chantelau E. *Br J OPhthalmol* **1998**:82:725-30
[6] Chantelau E ,Eggert H ,Seppel T , Schonau E ,Althaus C . *Br J Ophthalmol* **1997**:81:169-70.
[7] Borst,S.E; D.V.;Garzarella,L.;Vincent , K.;Pollock , B.P.;Lawenthal, D.T.;and Pollock,M.(**2001**). *Med & Sci In Sports Exerc*. 33(4):648-653.
[8] Cappon , J .;Brasel, J.A.;Mohan , S .;Cooper,D.M.(**1994**). *J Appl Physiol*.76(6):2490-2496.
[9] Gannon, G.A.,Rhind, S.G., Suzuki, M., Shek, P.N., Shephard, R.J., **1997**, *Can .J.Appl.Physiol.* 22, 2, pp;133-174.
[10] Steensberg,A.,Febbario,M.,vanHall,G.,Osada,T.,Sacchetti,M.,Saltin,B.,Pedersen,BK.,**2001**, *J.Physiol*.,537,pp:633-639.
[11] Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, Roubenoff R, Tucker KL, Nelson ME. *Diabetes Care.* **2002**; 25(12):2335-41.
[12] Dunstan DW, Daly RM, Owen N, Jolley D, De Courten M, Shaw J, Zimmet P. *Diabetes Care.* **2002**; 25(10):1729-36.
[13] Ostrowski,K., Rohde,T.,Asp,S.,SchjerLing,P .,Pederson, B.K.,**1999**, *J .Physiol*., 515, 1 ,pp:287-291.
[14] Lancaster , G.I.,Halson ,S.L.,Khan, Q.,.Drysdale ,P.,Wallace , F.,Jeukendrup,A.E.,Drayson, M.T.,Glesson, M , **2004**, *Exerc.Immunol.Rew*.,10,pp:94-102
[15] Haahr P, Pedersen B, Fomsgaard A, Tvede N, Diamant M, Klarlund K,Halkjaer-Kristensen J, Bendtzen K. *Int J Sports Med* 12: 223-227, **1991**.
[16] Braum, M.,Muller-Steinhardt,M.,Liesen,H.,Kirchner,H., **1997**, *Eur.J .Apply physiol*.,76,
[17] Surkina,I.D.,Danilenko,S.V.,Dudov ,N.S.,**1994**, *clin.Sci*.,87,6,pp:22-27.
[18] MC Dougall , D.,Sale, D.,Moro J.,Elder,G.,Sutton,J.,Howald, H.,**1979**, *Med.Sci.sports Exerc*.,11,pp:154-166.
[19] Soukup JT, Maynard TS, Kovaleski JE. *Diabetes Educ*. **1994**; 20(2):129-37.
[20] Eriksson J, Taimela S, Eriksson K, Parviainen S, Peltonen J, Kujala U. *Int J Sports Med*. **1997**; 18(4):242-6.
[21] Reckelhoff JF, Tygart VL, Racusen LC, Dzielak DJ: *Life Sci* 55:941–950, **1994**
[22] Flyvbjerg A: *Kidney Int* 5 2(Suppl. 60):S12–S19, **1997**

[23] Roy S, Sala R, Cagliero E, Lorenzi M: *Proc Natl Acad Sci* U S A 87:404–408, **1990**
[24] Bhaumick B, Danilkewich AD, Bala RM. *Diabetologia* **1986**;29:792–7.
[25] Averbukh EA, Weiss O, Yanko R, et al. *Diabetologia* **1997** 40(Suppl 1):A 493.
[26] Hyer SL, Sharp PS, Sleightholm M, et al. *Horm Metabol Res* **1989**;21:18–22.
[27] Hoeflich A., Reichenbach H.D., Schwartz J., Grupp T., Weber M.M., Foll J., Wolf E. *Domest Anim Endocrinol*. **1999**;17:39-51.
[28] Kraemer WJ & Ratamess NA. *Sports Med* **2005**; 35 (4): 339-361.
[29] Marx JO, Ratamess NA, Nindl BC, et al. *Med Sci Sports Exerc* **2001**; 33: 635-43.
[30] Nindl BC, Kraemer WJ, Marx JO, et al. *J Appl Physiol* **2001**; 90: 1319-26.
[31] Spiering BA, Kraemer WJ, Anderson JM, Armstrong LE, Nindl BC, Volek JS, and Maresh CM. *Sports Med* **2008**; 38 (7): 527-540.
[32] Pollard, Dr.,Gupta , K.,Mancino,L. and Hynie, I..*diabetologia* 25:56-59 ,**1983**.
[33] Rothe , H.,Hibino, T.,Itoh , Y., Kolb, H.and Martin , S. *Journal of Auto immunity* 10:251-256,**1997**.