The Effect of Moderate and High Intensity Endurance Trainings with Genistein on TNF- α and IFN- γ in Streptozotocin Induced Diabetic Rats

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Abstract

Objective: The purpose of this study was to investigate the effect of moderate and high intensity endurance trainings with genistein consumption on tumor necrosis factor alpha (TNF- α) and interferon gamma (INF- γ) in streptozotocin induced diabetic rats.

Materials and Methods: In this experimental study, 64 male diabetic rats were randomly assigned into 8 groups of 8 (1) first week control (2) last week control (3) moderate intensity endurance training (4) high intensity endurance training (5) genistein consumption, (6) moderate intensity endurance training and genistein consumption (7) high intensity endurance training and genistein consumption, and (8) sham (dimethylsulfoxide). Moderate and high intensity endurance trainings were performed on a treadmill at speeds of 10- 17 and 18- 22 m/ min for 8 weeks, 3 sessions per week, and 60 minutes per session. Genistein groups received 30 mg / kg of genistein per day peritoneally. Independent sample t-test, two-way analysis of variance and Bonferroni's post hoc test were used to analyze the findings (P-value≤ 0.05).

Results: Endurance training and genistein consumption had a significant effect on TNF-α reduction in streptozotocin-induced diabetic rats (P-value≤ 0.05); however, the effect of endurance training and genistein consumption on IFN-γ reduction was not significant (P-value≥ 0.05); also the interaction of training and genistein consumption in reducing TNF-α and IFN-γ was significant (P-value≤ 0.05).

Conclusion: It seems that endurance training and genistein consumption have interactive effects on decreasing the inflammatory factors in streptozotocin-induced diabetic rats.

Keywords: Training, Genistein, TNF- α, INF- γ, Diabetes

Introduction

Diabetes mellitus is a growing disease in the world that is associated with increased metabolic disorders such as disruption of fat metabolism, high blood pressure, high blood sugar, central obesity, and insulin resistance, and ultimately, cardiovascular risks (1). Diabetes is known as a debilitating disease due to its numerous outcomes and various disabilities among people (2,3). It has been clearly shown that increased adipose tissue, increases the secretion of anti-inflammatory cytokines such

as interleukin- 1β (IL-1β), interleukin- 6 (IL-6), interleukin- 8 (IL-8), tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) (4). Among these inflammatory factors, TNF- α and IFN- γ gene polymorphisms have potential for metabolic disorders, especially in type 1 diabetes mellitus. The researchers also argued that IFN- γ gene expression polymorphism, is a signal pathway in degradation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); in general, NF-κb is responsible for expressing the initiating proteins of necrosis and apoptotic proteins in cells (5,6). Many studies have been done on diabetes and its prevention and treatment methods. Among various studies, the effect of various sports activities on the control or treatment of this disease can be seen (7). Researchers believe that the immune system is affected by many changes in physiology and psychosocial factors. Physical activity has been introduced as one of the factors influencing the function of the immune system, so that the production of cytokines depends on the type, intensity and energy supply system during exercise (8); for example, eight weeks, three sessions per week of high intensity interval training and combined strength-endurance training had no significant effect on TNF- α and IL- 6 in women with diabetes mellitus (9). Twelve weeks, three sessions per week of moderate intensity aerobic training caused a significant decrease in IL- 6 and IL- 1β in women aged 50- 65 with metabolic syndrome (10); eight weeks, three sessions per week, and each session 15- 30 minutes of exercise, with an intensity of 50- 70 % of maximum heart rate, did not significantly decrease the levels of INF- γ in men 18 to 25 years of age (11); eight weeks, three sessions a week exercise with ergometer bicycle did not significantly alter the serum levels of IL- 6 and IL- 10 in women with type 2 diabetes (12); twelve months of exercise with a certain amount of calories has a greater effect on reducing INF- γ and TNF- α compared to low intensity aerobic exercises, high intensity aerobic exercises, and combined resistance exercises with aerobic exercise (13); sixteen weeks of resistance training resulted in a significant increase in TNF- α compared to endurance training, but resistance and endurance training had no significant effect on changes in INF- γ in rats (4). Considering the controversial results on the impact of exercise on the immune system in diabetic patients, studies show that diet and exercise alone or in combination reduce the progression of diabetes by 40 % after 6 years (14). Extensive research has been conducted on the effectiveness of medicinal plants used in traditional medicine on diabetic patients. The compounds in medicinal herbs such as nutritional fibers, vitamins, flavonoids, sterols and other antioxidant compounds, in addition to lowering blood lipids, can inhibit oxidation and release free radical of oxygen; they can also play an important role in developing the immune system and improving metabolic abnormalities in the body to treat this disease (15-17). Of these herbs, isoflavones derived from soy and its effects on some diseases have been considered by many researchers in recent years (17). Researchers believe that genistein interferes with cAMP accumulation and activation of PKA in insulin signaling, which improves insulin function and fat profile in diabetes (3,18). In this regard, receiving eight days of genistein at a dose of 600 mg / kg resulted in a significant decrease in NF- κb and TNF- α colonic injuries in mice (17); the use of genistein had a significant effect on reducing inflammatory factors such as IL- 6, TNF- α and NF- κb in the laboratory environment (19). Eight weeks daily consumption of genistein at a dose of 1 mg / kg of body weight resulted in a decreased expression of NF- κB and IL- 1β in ovarectomized diabetic rats (20); the use of genistein improved inflammatory activity and regulated expression of IL- 6, TNF- α in human stem cells (21). Genistein significantly increased nitric oxide and decreased IL- 6 (22). Despite the undeniable effects of physical activity on improving the quality of life of diabetic patients, exercise sciences

researchers have not yet been able to introduce an appropriate level of intensity of exercise to these patients. Also, due to the interest of the researchers in this field to the use of medicinal herbs in addition to sports activities and lack of sufficient information on the simultaneous effect of sport activities and the use of medicinal plants in reducing inflammation of diabetic patients; the present study was aimed at investigating the effect of moderate and high intensity endurance trainings with genistein consumption on the TNF- α and INF- γ in streptozotocin- induced diabetic rats.

Materials and Methods

To conduct this experimental study, 80 adult Sprague Dawley male rats, with a mean weight of 220.22± 25 gr, were purchased from the animal breeding center located at the house of animals of Islamic Azad University, Marvdasht Branch and transferred to the animal storage room of the sports physiology lab. During the whole study period, rats were kept at ambient temperature of 22± 2° C and controlled light (12-hour cycle of light and darkness) and maintained an eight-day adaptation period. Animal access to water and food was free during the research period (23). On day 8, after an overnight fast, rats were subjected to intraperitoneal injection of a single dose of 60 mg/ kg of streptozotocin (manufactured by the Sigma Company) dissolved in a citrate buffer (24). Four days after injection, blood samples were collected from the animals' tails using a glucometer to measure blood glucose (23). A total of 64 rats with blood glucose greater than 300 mg / dl were considered as the sample of study. The onset of the training program and the consumption of genistein proceeded one week after the induction of diabetes and maintenance of the rats. Based on the blood glucose, diabetic rats were randomly assigned into 8 groups of 8 including (1) first week control, (2) last week control, (3) moderate intensity endurance training, (4) high intensity endurance training, (5) genistein consumption, (6) moderate intensity endurance training and genistein consumption, (7) high intensity endurance training and genistein consumption, and (8) sham (received dimethyl sulfoxide as solvent of genistein). Genistein was manufactured by Hangzhou Dingyan Cem Co., Ltd with Batch No 20151105. It should be noted that in order to investigate the effects of diabetes induction on the research variables, 16 healthy male rats were selected and divided into two healthy groups of first week healthy control and last week healthy control. Rats in groups 3 and 5 ran on a treadmill for eight weeks, 3 sessions per week and 60 minutes each session at speeds of 10- 17 m / min, also rats in groups 4 and 7 ran on a treadmill for eight weeks, 3 sessions per week and each session 60 min at speeds of 18- 22 m / min (3,25). Groups 5, 6, and 7 received peritoneal injection of 30 mg / kg of genistein daily for eight weeks (26). After this period, blood samples were taken from rats to measure the variables of the study. Before blood collection, animals were kept fasting for 16 hours. To measure the serum levels of INF- γ, the Chinese Hangzhou Eastbiopharm business kit, with a sensitivity of 0.49 ng/ ml was used, and to measure the serum levels of TNF- α, the Chinese Hangzhou Eastbiopharm commercial kit with a scale of 1.52 ng/ L was utilized. Also, for analyzing the findings, independent sample T-test, two-way analysis of variance and Bonferroni's post hoc test were run, using SPSS software version 19 and a significant level of 0.05. It is worth noting that all ethical and legal aspects of this research have been reviewed and approved at Islamic Azad University, Marvdasht Branch. (IR.MIAU. REC.1396.123).

In order to conduct endurance training, animals were first placed on a treadmill to familiarize them with their endurance training protocols and then they ran at a speed of 8 m / min with a zero-degree gradient for 10 minutes. At the end of the treadmill, a very weak electrical shock was induced to force the animals to continue to move. To prevent potential damage by electrical shock, animals were conditioned from the beginning by

quietly treading the treadmill and creating a relatively weak sound or by touching the animal's tail. The endurance training protocol included 8 weeks of increasing running on a treadmill with zero-degree gradient (zero slope) at speeds of 10- 17 m / min and 18- 22 m/ min for 60 minutes per session and 3 sessions per week. To warm the animals during training sessions, animals after placing on the treadmill first ran at a speed of 8 m / min for 10 minutes, and then the training program was performed. Upon completion of the training program, in order to run the cooling program, the speed of the device was reduced inversely to reach zero. This program lasted about 5-7 minutes (3,25).

Results

In Table 1, the mean and standard deviation of the variables of research are presented in the ten groups of study. Independent sample t-test showed that induction of diabetes significantly increased the levels of TNF- α (*P*-value= 0.02) and IFN- γ (*P*-value= 0.004) in rats; 8 weeks of diabetes induction with streptozotocin has a significant effect on the increase of TNF- α (*P*-value= 0.01) and IFN- γ (*P*-value= 0.001) in diabetic rats. The levels of TNF- α (*P*-value= 0.01) and IFN- γ (*P*-value= 0.04) were significantly lower in the sham group than in the genistein supplementation group. The results of two-way analysis of variance in Table 2 indicated that endurance training (F= 12.99, *P*-value=0.001 and effect size 0.39) and genistein supplementation (F= 12.74, *P*-value= 0.001 and effect size 0.24) had a significant effect on TNF- α reduction in streptozotocin induced diabetic rats. Also, the interaction of endurance training and genistein consumption in the reduction of TNF- α was significant (F= 14.25, *P*-value= 0.001 and effect size 0.41). The results of Bonferroni's post- hoc comparison of means in Table 3 showed that endurance training with moderate intensity (*P*-value= 0.002) and high intensity (*P*-value= 0.001) had a significant effect on the reduction of TNF- α in streptozotocin induced diabetic rats. On the other hand, there was no significant difference in endurance training with moderate and high intensity (*P*-value= 0.99). The results of two-way analysis of variance showed that endurance training (F= 0.38, *P*-value= 0.68 and effect size 0.01) and genistein supplementation (F= 0.82, *P*-value= 0.36 and effect size 0.01) had no significant effect on reducing IFN- γ levels of streptozotocin induced diabetic rats. However, endurance training and genistein supplementation have interactive effects on reducing IFN- γ in streptozotocin induced diabetic rats (F= 10.56, *P*-value= 0.001 and effect size 0.34).

Discussion

The results of this study showed that induction of diabetes significantly affects the levels of TNF- α and IFN- γ in rats. Also, 8 weeks of diabetes induction with streptozotocin has a significant effect on the increase of TNF- α and IFN- γ in rats. Diabetes mellitus is one of the most common diseases and its rate is increasing rapidly. In this disease due to the relative or absolute lack of insulin, the metabolism of carbohydrates, proteins and lipids is disrupted (27); symptoms of inflammation include blood vessel dilatation,

Table 1. Levels of research variables in rats in research groups

Variable / Group	IFN-γ(ng/ml)	TNF-α (ng/L)
First week healthy control	21.15± 6.21	80.26± 18.10
Last week healthy control	17.51± 4.86	64.66± 16.93
First week diabetic control	12.65± 3.30	55.98± 20.02
Last week diabetic control	22.12± 5.32	84.18± 22.06
Moderate intensity endurance training	15.77± 7.17	41.70± 11.73
High intensity endurance training	11.52± 7.17	39.31± 7.08
Moderate intensity endurance training with genistein	20.53± 10.98	46.75± 21.73
High intensity endurance training with genistein	13.37± 4.50	34.78± 7.19
Genistein consumption	10.60± 1.73	39.71± 5.47
Sham	13.66± 3.76	65.15± 26.27

Table 2. Two-way analysis of variance analysis to examine the effect of moderate and high intensity endurance training with genistein supplementation on TNF- α and IFN- γ levels in streptozotocin induced diabetic rats

Variable	Factor	Sum of Squares	df	F	*P*-value	Effect size
TNF- α	Genistesin consumption	2439.19	1	12.74	0.001	0.24
	Endurance training	4975.15	2	12.99	0.001	0.39
	Interaction of endurance training and genistein consumption	5456.31	2	14.25	0.001	0.41
IFN- γ	Genistein consumption	30.48	1	0.82	0.36	0.02
	Endurance training	28.55	2	0.38	0.68	0.01
	Interaction of endurance training and genistein consumption	778.98	2	10.56	0.001	0.34

Table 3. Results of Bonferroni's post hoc test to compare the effects of moderate intensity endurance training and high intensity endurance training on levels of TNF- α in streptozotocin induced diabetic rats

Factor	No- training	Moderate intensity endurance training
High intensity endurance training	M= -23.70, *P*-value= 0.001	M= -4.75, *P*-value= 0.99
Moderate intensity endurance training	M= -18.91, *P*-value= 0.002	

increased capillary permeability along with high fluid leakage into inter- tissue spaces, migration of large numbers of granulocytes and monocytes into tissues and swelling of tissue cells. Some of the tissue products also cause these reactions, which include bradykinins, serotonin, prostaglandins, and the like. Some of these materials activate the macrophage system vigorously, and within a few hours macrophages begin to eat damaged tissues, but these macrophages sometimes cause more damage to tissue cells that are still alive. These cells produce different cytokines, including cytokines such as INF- γ, TNF- α, IL- 1β, IL- 6 and IL- 7, which increase in tissues (28). Bacterial lipopolysaccharide (LPS) is the most important inducer of TNF- α production. INF- γ produced by T and natural killer (NK) cells increases the production of TNF- α by macrophages stimulated by bacterial lipopolysaccharide (29). In line with the present study, the levels of INF- γ and TNF- α have been reported in patients with type 2 diabetes more than healthy subjects (13). Diabetes induction with streptozotocin increased TNF- α, IL- 6 and C-reactive protein (CRP) in rats (30). Also, inflammation is one of the known characteristics of diabetes, which increases levels of anti-inflammatory cytokines such as IL- 6, IL- 1 and TNF- α (31), so that IL- 1 activates NF- κb which causes differentiation of beta cells and calcium homeostasis in the endoplasmic network, absorption and activation of immune cells, and beta cell apoptosis (32). TNF- α decreases insulin effects by phosphorylation of insulin receptors (IR) tyrosine, which is the main substrate of IRS. There may also be several ways to activity of TNF- α on insulin and tyrosine phosphorylation. For example, TNF- α effect on protein kinase, which forces it to act on serine / tyrosine, or to disable serine / tyrosine phosphatases. TNF-α also strengthens insulin resistance by lowering the peroxisome proliferator-activated receptor gamma (PPAR- γ or PPARG) sensitivity, which is an important nuclear receptor that maintains insulin sensitivity naturally, and decreases expression of GLUT4 (33). Research has shown that with increasing body weight and metabolic abnormalities, TNF-α is more secreted in adipose tissue and leading to increased insulin resistance and increased mitochondrial permeability in cellular respiration and contamination of mitochondrial cytochrome (34), and as an inflammation mediator can inhibit insulin secretion from pancreatic beta cells (35). The results of this study showed that moderate and high intensity endurance trainings had a similar and significant effect on TNF- α reduction in streptozotocin induced diabetic

rats but did not have a significant effect on IFN- γ reduction in streptozotocin induced diabetic rats. A lot of studies have been done on the effects of training on INF- γ and TNF- α levels that have reported different results, for example, 12 weeks, three sessions per week, aerobic training with 60 % maximum oxygen uptake and combined training; two sessions per week with 70 % of 1RM and a combined training had the same effects on the reduction of serum levels of TNF- α in women with type 2 diabetes (36). Eight weeks of interval training with an intensity of 65- 75 % of heart rate reserve caused a significant decrease in TNF- α in men with metabolic syndrome (37); among the possible reasons for consistency of these studies with this study are the baseline levels of inflammatory factors and prolonged duration of the trainings for compatibility. 12 months of exercise with low calorie diet and a combination of resistance and endurance training reduced serum levels of INF- γ and TNF- α in patients with type 2 diabetes (13). This study was not in line with the reduction of INF- γ levels in the present study, but it was consistent with the decrease of TNF- α. Among the reasons for the consistency of these results with the results of this study, we can mention the similar intensity of long-term training periods as well as dietary control in both studies. 12 weeks of aerobic training reduced serum levels of INF- γ and TNF- α in elderly men and women (38); eight weeks of endurance training with an intensity of 50- 70 % of maximum heart rate significantly decreased INF- γ and did not change the serum levels of TNF- α significantly (8); among the reasons for the coherence of this study with the present study in TNF- α reduction, it is possible to mention the same intensity and duration of trainings in both studies. 10 weeks, three sessions training per week with 55- 75 % of maximum heart rate had no significant effect on TNF- α levels in obese women with type 2 diabetes (39); four weeks, three sessions resistance training per week with a specific ladder for rats had no significant effect on changes in serum levels of TNF- α in diabetic rats (30). The results of the above-mentioned studies were incompatible with the results of this study. The probable reasons for this could be the difference in the type of training in the present study with combined resistance and endurance, the use of special ladder for rats, as well as the difference in the selection of statistical population (human vs. animal subjects).

Researchers have pointed out in their studies that exercise activities improve the function of endothelial cells, and so reduce cytokine production in adipose tissue, muscle and mononuclear cells. Exercise activities also by indirectly increased insulin sensitivity, increased endothelial function, and reduced body weight reduce pro-inflammatory and inflammatory factors (37). Regular exercise activities stimulate Th2 activity and thus produce more Th2 cytokines, which, by increasing the production of anti-inflammatory cytokines, reduces inflammation. The response pattern of cytokines to exercise is very subtle. Due to the diverse application of cytokines and their rapid clearance of blood by surface receptors of immune cells, it is hard to justify its biological importance (8). Also, conflicting results have been reported on the mechanism of the effect of exercises on levels of INF- γ. However, various studies on humans and animals have shown that T-cells produce INF- γ in both the laboratory and the human body, which is stopped by cortisol and epinephrine hormones. These hormones (cortisol and epinephrine) increase during exercise and in response to exercise, so that epinephrine affects T cells at the level of the antigen presenting cells and also directly impacts T cell receptors. Catecholamines may also modulate immune responses. It is worth noting that the difference in changes in the levels of INF- γ following moderate and high intensity endurance trainings in the present study can be attributed to the intensity, type, and duration of training, and most importantly, the various effects of different trainings on the release of catecholamine and hormones such as cortisol and epinephrine (28).

The results showed that genistein supplementation had a significant effect on TNF- α reduction, but there was no significant effect on IFN- γ reduction in streptozotocin induced diabetic rats. Studies have been done on the effect of genistein on inflammatory factors. For example, the use of genistein in the in vitro environment did not have a significant effect on IFN- γ (40); Eight weeks consumption of one mg/ kg of body weight genistein had a significant effect on the reduction of NF- κb and IL- 1β and a significant increase in SIRT1 in ovarectomized and high fat diet and streptozotocin induced diabetic rats (16); Daily consumption of 30 mg/ kg of body weight genistein for eight weeks had a significant effect on the improvement of lipid profile in streptozotocin induced diabetic rats (3); on the other hand, incompatible with the current study, eight weeks consumption of 14 g soybean protein per day had no significant effect on changes in serum levels of TNF- α in peritoneal dialysis patients (41); among reasons for inconsistency, one can refer to the manner and dosage of genistein administered and a different statistical population. Also, the use of 50 mg/ kg of body weight genistein per day for two weeks did not significantly affect the reduction of TNF- α in the doxorubin induced nephropathy rats (42). Among the possible reasons for the inconsistency of this study with the present study, administration of different dosage in two studies and a different time period can be mentioned, which was eight weeks in the current study but two-week in the above-mentioned study. The use of 380 nMol of genistein in the cell culture medium reduced the expression of IFN- γ, and this decrease continued until 24 hours later (43). Reasons for the incompatibility of this study with the present study can be the type of study as well as the dosage of administration. Evidence suggests that diabetes and obesity increase TNF- α, which also causes inflammation. Inflammation by inhibiting the insulin receptor downstream cascade causes insulin resistance. On the other hand, when the cell is exposed to TNF- α with high levels of fatty acid, the phosphorylation of the serine member is inhibited. The inhibition and reduction of phosphorylation of the family member of the insulin receptor substrate (IRS) decreases the response of the cells to insulin because it is linked to insulin receptor and its intracellular signaling cascade pathway, and its inhibiting by TNF- α leads to insulin inhibition. Genistein, a member of the flavonoids family, has been shown to reduce inflammation with different pathways; researchers have argued that flavonoids inhibit inflammation by strongly inhibition of production of prostaglandin through the catalytic pathway of 5-lipoxygenase (44). In addition, the researchers pointed out that flavonoid genistein interferes with cAMP accumulation and PKA activation, and hence affects insulin signaling. In fact, flavonoids, by eliminating free radicals, have a protective effect against lipid peroxidation; they can modulate the endothelial nitric oxide metabolism that leads to NO radical production as well as NADPH oxidase. As a result, genistein by improving glucose tolerance and insulin resistance, can facilitate activation of Akt and consumption of glucose, and reduce oxidative stress and AMP kinase (3). However, the main anti-inflammatory effects of genistein can be attributed to the mechanism of fat mass and to the reduction of pro-inflammatory factors, such as IL- 1β, and its simultaneous expression with NF- κb, so that genistein by inhibiting IκBα-inhibiting proteins, increases the phosphorylation of IKK (an enzyme that inhibits the IκB protein), and phosphorylation of IL- 1β receptors leads to a decrease in TNF- α production (20, 45).

The results showed that endurance training and genistein supplementation have interactive effects on reducing TNF- α and IFN- γ in streptozotocin induced diabetic rats. Despite investigations by the researcher, there has been no study to investigate the interactive effect of genistein and endurance training on TNF- α and IFN- γ. However, the researchers found in their research that in the explanation of

interactive reducing effects of inflammatory factors, genistein and endurance training in diabetic rats could be effective, for example, eight weeks, three sessions per week, and 60 minutes per session moderate intensity endurance training and 30 mg/ kg of genistein consumption had an interactive effect on the improvement of lipid profile of streptozotocin induced diabetic rats (3); Eight weeks, three sessions per week of endurance training with moderate intensity and daily consumption of 100 g of soybean nuts were observed to decrease the mean systolic and systolic blood pressure in obese menopausal women (46); on the other hand, inconsistent with the present study, 30 sessions of combined training (aerobic and resistance) and 100 mg of isoflavone per day did not have interactive effects on the reduction of inflammatory factors (IL- 6 and IL- 8) in postmenopausal women (47); one of the possible reasons for the inconsistency of this study is the difference in the statistical population and the initial levels of inflammatory factors measurement. The results of studies showed that genistein and endurance training both with decreasing fat mass and subsequently reducing the pro-inflammatory factors from the signal pathway of inhibiting the IκBα protein, increasing the phosphorylation of IKK and reducing the expression of Nf- κb, as well as through the phosphorylation of IL- 1β receptors lead to a decrease in TNF- α production; and a decrease in the expression of NF- κb results in increased expression of BDNF (10,20,37,45). Nevertheless, it seems that the insignificant effect of moderate and high intensity endurance trainings and genistein consumption separately on the reduction of IFN- γ can be due to the intensity and dose of administration of these two interventions. Among the limitations of this research were the lack of control on training- induced stress and biological behaviors affecting inflammatory factors. Considering the effect of intensity of trainings on the rate of inflammation and antioxidant properties of genistein and disregarding higher doses along with various endurance training, it is recommended to investigate the effect of using higher doses of genistein on anti-inflammatory agents such as IFN- γ.

Conclusions

Regarding the results of this study, it seems that endurance training and genistein consumption have interactive effects on reducing inflammatory factors in streptozotocin induced diabetic rats.

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Conflict of Interest

We declare that there was no conflict of interest.

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