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The Effect of Moderate Intensity Continuous Training (MICT) on TNF-α and Fetuin A in Type 2 Diabetic Wistar Rats

Tahereh Vahdati [1], **Rahman Soori** [1]✉, **Ali Akbarnezhad** [1], **Parisa Pournemati** [1]

[1] Department of Exercise Physiology, Faculty of Sport Sciences and Health, University of Tehran, Tehran, Iran

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✉ ***Correspondence to:***
Rahman Soori
Department of Exercise Physiology, Faculty of Sport Sciences and Health, University of Tehran, Tehran, Iran

Email:
Soori@ut.ac.ir

A B S T R A C T

Introduction: Hepatokines secreted by the liver play a pivotal role in the pathogenesis of type 2 diabetes, directly influencing glucose and lipid metabolism. Exercise training is recognized as an effective treatment strategy for type 2 diabetes. This study aims to investigate the impact of moderate intensity continuous training (MICT) on the levels of Fetuin-A and tumor necrosis factor-alpha (TNF-α) in type 2 diabetic rats.

Material & Methods: Fifteen male Wistar rats aged between 8 and 10 weeks were randomly assigned to three groups (5 rats in each group): healthy control, diabetic, and training diabetic. Diabetes was induced through intraperitoneal injection of nicotinamide and streptozotocin (STZ). The MICT protocol involved eight weeks of continuous running, five days per week, at 55-60% of maximal oxygen consumption. Blood samples were collected 48 hours after the last training session, and serum levels of TNF-α and Fetuin-A were measured.

Results: The observed reductions in Fetuin-A, TNF-α, and glucose levels were not statistically significant in the trained group compared to the diabetic group. However, a significant decrease in insulin levels (p=0.002) and insulin resistance (p=0.01) was observed in the trained group compared to the diabetic group.

Conclusion: In conclusion, moderate intensity continuous training, as a non-pharmacological intervention, appears to play an effective role in the management of type 2 diabetes by improving insulin resistance and reducing insulin levels.

Keywords: Moderate Intensity Continuous Training (MICT), Fetuin-A, Tumor Necrosis Factor Alpha (TNF-α)

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Introduction

Fetuin A is a hepatokine secreted by the liver, known to be associated with insulin resistance, obesity, and type 2 diabetes mellitus (1). This phosphorylated glycoprotein acts as an inhibitor of insulin receptor tyrosine kinase, fostering insulin resistance in skeletal muscle and liver cells. Additionally, Fetuin A is implicated in promoting inflammatory responses. As a ligand for Toll-like receptor (TLR) and a factor in macrophage polarization, it converts macrophages from an anti-inflammatory phenotype (M2) to an inflammatory phenotype (M1). Through direct interaction with macrophages and the activation of Monocyte Chemoattractant Protein-1 (MCP1) and Inducible Nitric Oxide Synthase (iNOS) via the cJun/JNK–IFN-γ–STAT1–Nox4 pathway, Fetuin A triggers an inflammatory cascade, stimulating the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α).

TNF-α plays a critical role in the signaling process, disrupting tyrosine phosphorylation of the insulin receptor, diminishing the activity of the lipoprotein lipase enzyme (LPL), and contributing to insulin resistance and the development of type 2 diabetes. Ultimately, the inflammatory response induced by Fetuin A culminates in non-alcoholic fatty liver, adipose tissue inflammation, beta cell apoptosis, insulin resistance, and the progression of type 2 diabetes (2).

Fetuin A has been identified as positively correlated with impaired glucose tolerance, hepatic fat accumulation, and insulin resistance, exhibiting a significant negative correlation with insulin sensitivity. Moreover, its plasma levels are markedly elevated in individuals with type 2 diabetes compared to those without the condition (3). Studies have demonstrated that inhibiting Fetuin A can enhance insulin signaling pathways in the liver and skeletal muscle, concurrently improving insulin activity, glucose tolerance, and preventing weight gain induced by a high-fat diet (3,4).

Despite the observed stimulation of tumor necrosis factor-alpha (TNF-α) by Fetuin A, contrasting findings exist in the literature. One study involving diabetic and non-diabetic patients with varying body mass indices indicated a negative relationship between serum levels of Fetuin A and TNF-α in diabetic patients (5). However, another study conducted on 172 patients with type 2 diabetes and complications of microangiopathy established a positive correlation between the serum levels of Fetuin A and TNF-α in diabetic patients (6). These divergent results underscore the complexity of the interactions involving Fetuin A and TNF-α in the context of diabetes.

Exercise training has the potential to modulate the accumulation and secretion of adipokines, hepatokines, and cytokines, thereby influencing metabolic diseases (7). Aerobic exercise, in particular, is known to activate the intracellular AMPK (AMP-activated protein kinase) pathway. This activation is observed in the liver during exercise, suggesting that the adaptive response mediated by AMPK may suppress hepatic glucose production, making it an effective strategy in the management of type 2 diabetes (8, 9).

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Given the substantial association between type 2 diabetes and Fetuin A, numerous studies have reported a reduction in Fetuin A levels with various types of exercise in individuals with type 2 diabetes (10-12). However, contradictory results in studies examining the impact of exercise training on Fetuin A levels suggest that the precise role of exercise in regulating Fetuin A remains incompletely understood (13).

While there has been no specific investigation into the activation of pro-inflammatory cytokines, such as TNF-α, by Fetuin A and the subsequent effects of exercise on them, related studies have explored the impact of exercise on TNF-α and Fetuin A. One study in diabetic patients demonstrated a significant decrease in the levels of both Fetuin A and α-TNF in individuals who engaged in regular exercise (14). Recognizing that pro-inflammatory cytokines alone can contribute to the inflammation associated with type 2 diabetes (15), regular exercises like swimming and treadmill activities have been shown to inhibit pro-inflammatory cytokines while promoting anti-inflammatory cytokines (16). In support of this, research on various types of exercise training suggests that aerobic exercise in type 2 diabetic patients can significantly reduce TNF-α, C-reactive protein (CRP), and Interleukin 6 (IL-6) (17).

Most previous research on Fetuin A has focused on its examination in blood serum; however, this study uniquely investigates Fetuin A levels in liver tissue. Furthermore, there is a limited number of studies in Iran exploring the impact of exercise training on hepatic hepatokines, particularly Fetuin A, and its influence on TNF-α in individuals with type 2 diabetes. To address this gap, we opted to evaluate the effects of moderate intensity continuous training (MICT) in a type 2 diabetic Wistar rat model. The primary objective of this study was to assess the impact of 8 weeks of MICT on hepatic hepatokine Fetuin A and cytokine TNF-α in type 2 diabetic Wistar rats. This research design aimed to contribute valuable insights into the specific interplay between exercise, hepatic factors, and inflammatory cytokines in the context of type 2 diabetes.

Materials and methods

Animal Samples

The current study was a fundamental-experimental type, which was conducted with the general aim of investigating the effect of 8 weeks of moderate-intensity continuous training on the levels of hepatic Fetuin A and serum α-TNF in Wistar rats with type 2 diabetes. By reviewing and studying past articles, 20 male Wistar rats with an average weight of 220 ± 20 grams; They were purchased from the animal care center of Pasteur Institute of Iran, among them, one of the mice died and 2 other mice did not become diabetic, and finally 15 mice were included in the study. Rats were kept in the animal facility of the Faculty of Physical Education and Sports Sciences, University of Tehran, under temperature conditions of 22 ± 3 °C, humidity 45-55%, and light-dark cycle 12-12. They had water (300 ml bottle) and enough food (Behparvar Iran Company) at their disposal.

After a week of acclimatization and familiarization with the environment, the rats were randomly divided into 3 groups:

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healthy controls, diabetics, and diabetics with moderate intensity continuous training, and they were fed freely with standard food until the end of each experiment. To induce type 2 diabetes, 15 minutes after the induction of nicotinamide (Qualichems) with an amount of 121 mg/kg animal weight, the prepared solution of streptozotocin STZ (Streptozotocin) (Sigma Aldrich) in citrate buffer (PH=4.5) It was injected intraperitoneally with a dose of 60 mg/kg of animal weight. After 72 hours, mouse blood sugar was measured by Performa small glucometer, and blood was taken from the tip of the mouse's tail. A blood glucose level of less than 126 mg/dL was considered as a criterion to confirm the diagnosis of type 2 diabetes in mice.

Training method

Before initiating the training protocol, rats in the training group underwent a 1-week treadmill adaptation phase, involving progressive running at low intensity, ranging from 6 to 25 meters per minute. The formal training program spanned 8 weeks, with 5 sessions per week. Each training session commenced with a 5-minute warm-up at low intensity. During the initial week, the rats trained for 20 minutes at a speed of 25 m/min, gradually progressing to a speed of 30 m/min for a duration of 60 minutes in the eighth week. The training intensity was maintained at 55-65% of the maximum oxygen consumption (VO2max). Following the completion of each training session, a 5-minute cooldown at low intensity was implemented (18). Refer to Table No. 1 for a detailed overview of the training protocol.

Measurement methods

After a 12-hour fasting period and 48 hours post the completion of the 8-week training regimen, the mice were sacrificed to assess the impact of Moderate Intensity Continuous Training (MICT) on hepatic hepatokine Fetuin A from liver tissue and serum levels of α-TNF. Anesthesia was induced by intraperitoneal injection of 10% ketamine (85 mg/kg) and 2% xylazine (10 mg/kg). Subsequently, liver tissue was swiftly isolated, frozen, and stored at -80°C for subsequent histological examination. Blood samples were collected and subjected to centrifugation at 3000 rpm for 15 minutes to separate the serum. The serum samples were then frozen in a nitrogen tank and stored at -80°C for further analysis, pending transport to the laboratory.

Western blot

Protein lysates were prepared by using lysis buffer containing 500 mM Tris (pH 8), 0.08 g sodium chloride, 1% NP-40, 0.025 g sodium deoxycholate, 1% SDS, and 0.003 g EDTA, which were separated from Subcutaneous White Adipose Tissue (SCWAT). The protein lysates underwent centrifugation at 12,000 g for 10 minutes at 4°C. The protein concentration of the supernatant was determined using the Bradford method. Following denaturation with a 12% prepared gel (Bio-ad, Hercules, CA, USA) in the sample, the proteins were separated via SDS polyacrylamide gel electrophoresis and subsequently transferred onto a polyvinylidene difluoride (PVDF) membrane (Roche, Sussex, England). The membrane was blocked for 1 hour and 15 minutes in 2% milk in TBST (Tris-buffered saline and 0.1% Tween20). Blots

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were incubated overnight at 4°C with the primary antibody:

Fetuin-A (H-8) (sc-166531 AC) (1:300)

Following the blocking step, the membrane was washed three times with TBST buffer, each time for 15 minutes. Subsequently, the membrane was incubated with an anti-rabbit secondary antibody (dilution 1:1000) for 1 hour and 15 minutes at room temperature in TBST. Protein bands were visualized using a detection reagent (ECL), and the intensity of the bands was measured utilizing the striping method with a radiology film (Fuji).

ELISA

In accordance with the specifications of the enzyme-linked immunosorbent assay kit, we utilized the rat INS (Rattus norvegicus) matching antibody pair kit to assess the relative levels of TNF-α, insulin, and glucose in rat serum.

Calculation of HOMA-IR

The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) equation was employed to calculate the insulin resistance index.

HOMA- IR = (Fasting glucose mg/dl (x (fasting insulin) 405 μU/ml)

Statistical Analyses

The data were analyzed using SPSS software version 26. Analysis of variance was employed for inferential analysis of findings, and Tukey's method was utilized for two-way comparisons between groups. Pearson's test was also conducted to examine relationships. A significance level of 0.05 was applied for all statistical analyses. Details of the exercise training program are provided in Table 1.

Table 1. Moderate-Intensity Continuous Training (MICT) Program for Eight Weeks.

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Duration (minutes)	20	40	60	60	60	60	60	60
Speed (meter per min)	25	25	25	30	30	30	30	30
Slope (degrees)	0	0	0	1.5	3	4.5	6	9

Results

As indicated in Table 2, based on the results of the analysis of variance, no significant differences were observed in the serum levels of TNF-α (P=0.115) and liver levels of Fetuin A (P=0.287) between the groups.

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Table 2. Mean ± Standard Deviation of Serum TNF-α and Liver Fetuin A Values, along with Metabolic Components in Groups.

Metabolic Components	Diabetic Number=5	Training Diabetic Number = 5
Fetuin A	2.186 ± 0.781	1.482 ± 0.430
TNF-α	196,000 ± 57,974	130.600 ± 50.396
Glucose (mg/dL)	365.400 ± 127.239	225.400 ± 97.577
Insulin (ng/mL)	3.080 ± 0.432	1.700 ± 0.539*

ANOVA analysis was employed to examine variance between groups. * denotes a significant difference between the diabetic group and the training diabetic group at a significance level of $p < 0.05$

The one-way analysis of variance test revealed that the serum level of TNF-α in the training group was lower than in the diabetic group (P=0.093), but this decrease did not reach statistical significance. Similarly, the analysis of Fetuin A by one-way analysis of variance did not demonstrate a significant difference between the diabetic (P=0.115) and training groups. While serum glucose levels (P=0.087) showed no significant difference between the two groups, serum insulin levels (P=0.002) and insulin resistance index (P=0.010) were significantly different.

Furthermore, the Pearson correlation coefficient test indicated a strong correlation between Fetuin and glucose (P=0.010) and the insulin resistance index (P=0.006). However, it did not reveal significant correlations between Fetuin A and TNF-α (P=0.938), Fetuin A and insulin (P=0.158), TNF-α and glucose (P=0.890), TNF-α and insulin (P=0.179), as well as TNF-α and the insulin resistance index (P=0.445) (Table 3).

Table 3. Pearson Correlation Coefficient Values between Fetuin A, TNF-α, and Metabolic Components.

Variable	TNF-α (g/dl)	Glucose (mg/dl)	Insulin (nanograms/ml)	Insulin resistance
Fetuin A	0.938	0.010	0.158	0.006
TNF-α	0.938	0.890	0.179	0.445

Discussion

The research findings revealed a notable 32% decrease in glucose levels within the trained group compared to the diabetic group. Additionally, fasting insulin levels and insulin resistance exhibited reductions of 71% and 58%, respectively, in the trained group as compared to the diabetic group.

In the context of Fetuin A analysis, it was observed that continuous training with moderate intensity led to a decrease in serum levels of Fetuin A in rats with type 2 diabetes; however, this reduction did not reach statistical significance. Similar

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observations were reported in a study involving 27 diabetic patients, where no changes in serum Fetuin A were noted after 3 months of aerobic activity (19). Conversely, Sakr et al.'s study, conducted on 60 rats, demonstrated a significant decrease in serum Fetuin A after 16 weeks of swimming in rats with metabolic syndrome (20). Another study by Keihanian et al. on humans showed a significant reduction in serum Fetuin A after 8 weeks of aerobic and resistance training in diabetic patients (21).

It is worth noting that factors such as disease status (fatty liver, diabetes, and obesity), drug use, and higher training intensity (e.g., HRmax 85%) may play crucial roles in influencing the levels of Fetuin A (22).

Fetuin A is recognized as an inflammatory mediator and is believed to play a crucial role in systemic insulin resistance (23, 24). Our study demonstrated a substantial correlation between liver levels of Fetuin A and the indices of insulin resistance and glucose, aligning with the findings of Diack's study conducted on mice (25).

Consistent with our results, Bradley observed a significant decrease in insulin resistance following 6 weeks of exercise training, suggesting a positive impact on insulin sensitivity through the reduction of inflammatory factors in adipose tissue (26). In essence, our research indicates an improvement in glycemic control indicators through exercise training, reinforcing similar findings reported in related studies.

Another study, conducted with obese elderly subjects, demonstrated a reduction in Fetuin A levels after 12 weeks of exercise training, five days per week, at 85% HRmax. This decrease was associated with decreased resistance to hepatic insulin (27). The correlation between Fetuin A and insulin resistance in the liver was found to be significant with exercise training. Consequently, the reduction in Fetuin A induced by exercise, independent of systemic changes in inflammation, is primarily linked to hepatic glucose production (28). Malin et al. emphasized the role of Fetuin A in the insulin resistance of skeletal muscles, suggesting that the decrease in Fetuin A may contribute to improved glucose tolerance through exercise training in patients with fatty liver (10).

In general, long-term exercise training is associated with a decrease in Fetuin A and Free Fatty Acids (FFAs), resulting in diminished Toll-like Receptor 4 (TLR4) signaling and subsequently improved insulin sensitivity (28). Fetuin A, through the inhibition of AKT phosphorylation, 160AS inhibition, and hindering the translocation of intracellular GLUT-4 (Glucose transporter type 4) to the plasma membrane, reduces glucose uptake in skeletal muscle. This disruption in insulin signaling pathways contributes to conditions such as obesity, insulin resistance, and non-alcoholic fatty liver disease (29, 30).

Conversely, exercise training has been shown to elevate membrane GLUT-4 expression in both animal and human studies (31), enhancing insulin signaling (32). The findings suggest that Fetuin A, either directly or indirectly, hampers GLUT-4 turnover, contributing to improved glucose disposal post-exercise (24).

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An elevation in Fetuin A levels is known to induce excess fat accumulation in the liver and adipocytes by promoting the phosphorylation of mTOR (Mammalian target of rapamycin), consequently increasing SREBP-1C expression and triggering lipogenesis. Ultimately, these bioenergetic disturbances in lipogenesis contribute to hepatic steatosis, Non-Alcoholic Fatty Liver Disease (NAFLD), insulin resistance (IR), and the onset of type 2 diabetes (33).

Although SREBP-1C was not directly evaluated in our study, a separate investigation on rats fed a fatty diet and subjected to 12 weeks of aerobic exercise on a treadmill revealed a significant reduction in SREBP-1C gene expression (34).

Considering the known stimulation and activation of α-TNF by Fetuin A in diabetic patients (35) and the increase in α-TNF production and secretion due to inflammation caused by type 2 diabetes (36), we anticipated a significant decrease in the serum level of α-TNF in the exercise group compared to the diabetic group. However, contrary to expectations, the level of this cytokine was lower but not statistically significant.

Several studies have highlighted the detrimental role of elevated α-TNF in glucose metabolism, linking it to beta cell failure (37). This cytokine directly impedes glucose uptake stimulated by peripheral insulin by inhibiting Akt160 substrate phosphorylation, contributing to insulin resistance (39). Thus, an abnormal reduction in α-TNF levels is essential in type 2 diabetes. Previous research has demonstrated that exercise training can significantly reduce α-TNF levels in type 2 diabetic patients, effectively mitigating the inflammatory state associated with type 2 diabetes and alleviating the damage caused by α-TNF to beta cells (40).

However, conflicting studies exist, such as Martin et al.'s observation in animal samples with metabolic disorders where α-TNF levels increased after aerobic exercise (41). Some studies reported no change in α-TNF levels following relatively long-term exercise training; for instance, in a study on type 2 diabetic patients undergoing 12 weeks of aerobic exercise three times a week, despite a significant decrease in insulin resistance and blood glucose, α-TNF levels did not exhibit a significant change post-exercise (42). Another study on rats reported that the levels of α-TNF, IL-6, and IL1B remained unchanged after 8 weeks of aerobic exercise performed five days a week (43).

Few studies have explored the impact of exercise on Fetuin A and α-TNF. The results of our research indicate no correlation between Fetuin A and α-TNF, suggesting that α-TNF may be locally produced in vessels and primarily acts in a paracrine manner (44). A study by Chan-Hee-Jung revealed a correlation between Fetuin A levels and α-TNF in diabetic patients with nephropathy, implying that the α-TNF-stimulated inflammatory reaction might be associated with Fetuin A in type 2 diabetes patients (45). Additionally, another study reported a negative relationship between Fetuin A plasma levels and α-TNF in diabetic patients (5). However, reports also suggest that Fetuin A increases α-TNF expression and suppresses adiponectin synthesis from

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adipocytes, indicating a potential contribution to chronic inflammation (44). It is noteworthy that none of the mentioned studies investigated the impact of exercise training, making it challenging to comprehensively understand the role and significance of training in diabetes treatment.

Despite the limitations of our study, such as the inability to directly measure VO2max and a relatively small sample size, the results contribute to a better understanding of factors influencing type 2 diabetes. This could offer practical solutions for improved disease management and complication prevention. Considering both consistent and inconsistent research findings, it is plausible that the type, intensity, participants' health status, and duration of exercise play a role in the studied factors. Nutrition type and daily intake are also crucial aspects that merit investigation in future research. Our study focused on moderate-intensity continuous training, suggesting the need for exploring different exercise types, including resistance, aerobic, and combined, to provide optimal non-pharmacological solutions for beneficial effects on type 2 diabetes patients.

Conclusion

The findings from this study demonstrate that engaging in continuous moderate-intensity exercise can effectively lower Fetuin A levels. Additionally, it exerts a significant impact on glycemic indices, playing a crucial role in the control and treatment of type 2 diabetes by enhancing insulin sensitivity and reducing insulin resistance.

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Conflict of interest

The authors declare that no conflicts of interest exists.

Authors’ contributions

T.V and R.S contributed to selecting the research title and designing the training protocol. R.S and A.A conducted diabetes induction. Additionally, T.V and P.P executed the training program and monitored animals. All authors participated in data collection, and each contributed to writing sections of the paper. The final manuscript was reviewed and confirmed by all authors.

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