Journal of Sports Physiology and Athletic Conditioning (J.S.P.A.C) 2025; 5 (15): 44-61

Research Article

Nettle Supplementation Augments the Benefits of Combined Training on blood Glucose control and inflammatory factors in women with type 2 diabetes

Solmaz Babaei Bonab [1*], Samaneh Dastah*[2]

1. Associate Professor of Exercise Physiology, Faculty of Sport Sciences, University of Maragheh, Maragheh, Iran
2. Assistant Professor of Exercise Physiology, Faculty of Sport Sciences, University of Maragheh, Maragheh, Iran

Received: 18 February 2025
Revised: 12 March 2025
Accepted: 12 April 2025

Keywords:
Functional Stretching, Extra Functional Stretching, dorsi Flexion, Plantar Flexion.

Abstract

Background: Although consumption of nettle can change the inflammatory response in diabetic patients and may increase the benefits of exercise, no research has yet quantified the simultaneous effect of exercise and consumption of nettle on inflammatory indicators in diabetic patients. This research aims to investigate the effects of 12 weeks of combined training with nettle consumption on inflammatory factors in women with type 2 diabetes

Materials and Methods: The participants (N=60) were randomly distributed into four groups, each consisting of 15 participants: Combined Training group (Com), Nettle Supplement group (NS), Combined Training + Nettle Supplement (Com+NS), Control Group. The intervention comprised a 12-week treatment involving Nettle supplementation, a 12-week combined training (aerobic resistance-periodic) protocol with three sessions per week. Serum levels of blood glucose, insulin, HOMA-IR, CRPT3, IL-1β and IL-33 were measured within 48 h of the before and final training session.

Results: Statistical analyses revealed significant differences across all measures among the groups ($p < 0.05$). The combined training and supplementation approach led to notable reductions in blood glucose (p=0.001). Furthermore, CTRP3 and IL-33 levels in the three intervention groups were significantly increased compared to the control group (p=0.001). Also, there was a significant decrease in IL-1β levels in the Com, NS, and Com + NS groups relative to the control group (p=0.001).

Conclusion: This investigation underscores the potential of Nettle supplementation and Combined training as a synergistic strategy to ameliorate diabetes-related complications and enhance overall metabolic health in women with type 2 diabetes.

***Corresponding author:** Solmaz Babaei Bonab, Samaneh Dastah
Address: Department of Exercise Physiology, Faculty of Sport Sciences, University of Maragheh, Maragheh, Iran
Email: s.babaei@maragheh.ac.ir - s.dastah@maragheh.ac.ir **Tell**:
SBB: 0000-0003-0185-7850- SD: 0000-0002-7949-3527

1. Introduction

Inflammation is one of the most important causes of diabetes, which is associated with an increase in proinflammatory cytokines and decrease anti-inflammatory that intensifies insulin resistance by activating systemic pathways of insulin sensitivity and glucose homeostasis (1, 2). Some studies have suggested that the development of insulin resistance and type 2 diabetes is influenced by inflammatory mediators and some cytokines (1, 3). Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine that is secreted in response to inflammation and is a limiting and reversing factor in the inflammatory process (4). Research has reported that IL-1β is elevated in diabetics and interferes with insulin signaling (5, 6). In type 2 diabetes, insulin resistance can be reduced by suppressing inflammation and reducing IL-1β activity (7). On the other hand, inflammation due to metabolic disorders is associated with a decrease in anti-inflammatory cytokines, including Interleukin-33 (IL-33) (8-10). IL-33 is released after cell damage and as a negative regulator of Nuclear Factor Kappa B (NF-KB) gene transcription not only increase cytokine production from helper T cells, but also activity They also reduce natural killer (NK) cells and regenerate oxidation products, thus IL-33 act as a protective agent against insulin resistance, diabetes mellitus and obesity (10, 11). Increased IL-33 expression has been shown to improve fasting blood glucose and glucose tolerance (9, 10). In contrast, its removal and removal may increase the cytokine toxicity of natural killer cells and release inflammatory factors, leading to increased insulin resistance (9, 10). Also, adipokines produced in adipose tissue can have a significant effect on glucose and fat metabolism in the form of autocrine and paracrine (12, 13). CTRP3 is a potent anti-inflammatory adipokine that inhibits inflammatory pathways induced by lipopolysaccharides, fatty acids, and Toll-like receptor (TLR) ligands in adipose tissue (14).

In addition, this protein plays an important role in lowering glucose and inhibiting gluconeogenesis in liver tissue. It can also improve insulin sensitivity, reduce pro-inflammatory factors, and improve endothelial function (15). Serum CTRP3 levels have been shown to be significantly reduced in patients with type 2 diabetes compared to the healthy control group (16). These findings indicate the potential role of CTRP3 as a diagnostic and predictive tool in diabetes and cardiovascular disease.

Therapeutic aims in diabetes mainly include stimulating insulin secretion and reducing insulin resistance through lifestyle changes and diets, training, and the use of herbal medicines containing antidiabetic agents (17). Nettle is one of the herbal medicines that has been introduced in traditional medicine as an anti-diabetic medicine (18-20). This plant has been reported to have anti-allergic, antioxidant, anti-hypertensive, anti-hypercholesterolemic and hepatoprotective properties (21, 22). Nettle consumption has been shown to improve hyperglycemia in patients with type 2 diabetes (23).

In addition, the effect of regular training on the improvement of type 2 diabetes, which positively regulates plasma anti-inflammatory cytokines and negatively regulates pro-inflammatory cytokines, has been reported (4, 7). It seems that combined training programs due to the dual effects of the compensatory mechanisms of both types of training methods, further improve insulin sensitivity.

Considering the anti-inflammatory and antioxidant effects of nettle as well as exercise, it seems that the interaction of these two cases and the study of this supplement with exercise has significant anti-inflammatory effects, a change that may minimize the risk factors associated with metabolic diseases.

Because studies in this area are limited; The present study aims to investigate the effect of 8 weeks of combined combination training (aerobic resistance-periodic) with nettle consumption on the expression of CTRP3, IL-1β, serum levels of IL-33 and blood glucose in women with type 2 diabetes.

2. Materials and Methods

Participant

This study was performed on middle-aged women with type 2 diabetes referred to the Tabriz Diabetes Association. In this study, out of 182 initial patients after reviewing the entry and exit conditions of the study, 102 people were excluded from the study due to lack of entry requirements, and 12 people were excluded from the study due to cancellation of the research. The remaining 68 people were randomly divided into four equitably sized groups (15 participants in each group) by computer software (computer-generated random number system): 1: Combined Training (resistance training and periodic aerobic training) (Com), 2: Nettle Supplement Group (NS), 3: Combined Training + Nettle Supplement Group (Com+NS) 4: The Control Group (Control) were included (consort chart) (figure 1). Inclusion criteria included female gender, type 2 diabetes, BMI ≥28, age between 50-60 years, HbA1C more than 6.5%, fasting blood sugar equal to or more than 126 mg/dl. Subjects had no other chronic illness and history of exercise for the past 6 months, myocardial infarction, uncontrolled arrhythmia, severe hypertension, and diabetic complications such as diabetic foot ulcer, nephropathy, or diabetic retinopathy. Also, the criteria for excluding the subjects from the study, including an unwillingness to continue cooperation in the research, consumption of dietary supplements and weight loss,irregular participation in exercise programs, and injury were considered. The training protocol of the present study was combined training and the intensity of training was designed based on the sports recommendations of diabetic patients (34, 35). Resistance exercises along with periodic aerobic exercises were performed for twelve weeks, three sessions per week with a gradual

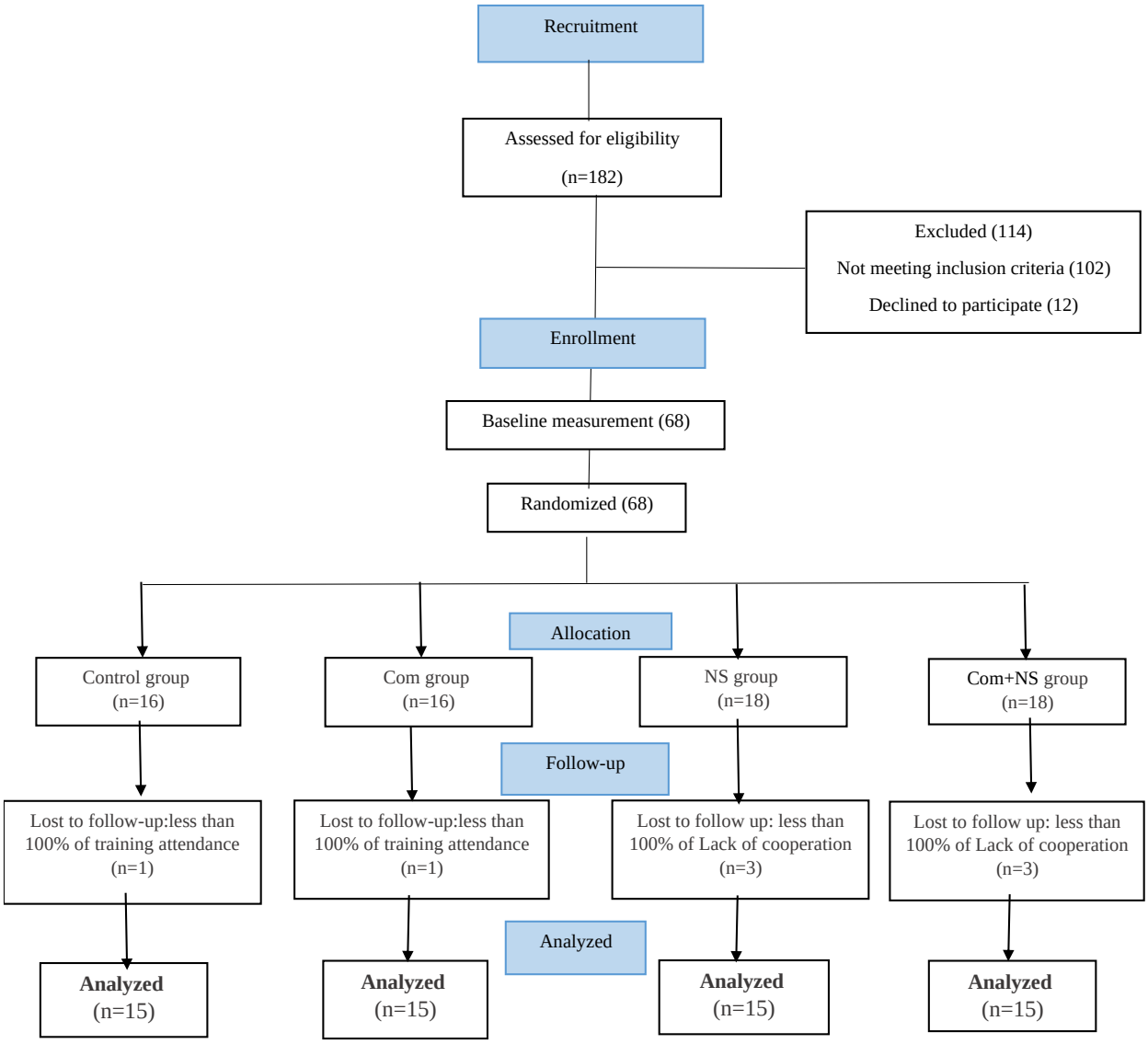

Figure 1. Participants' flow chart

It is worth noting that all subjects were examined by a physician and attended all physician practice sessions. All participants also completed and signed an informed consent form. This research with the code IR.SSRI.REC-1400-1242 was approved by the ethics committee.

Week	Warm-up (minutes)	aerobic interval training (MHR)	Resistance training (1-RM)	Cooling (minutes)
1st	15	20 minutes Training: 60 seconds with 60% MHR Rest: 60 seconds with MHR 50%	First set: 1-RM 30% up to 10 repetitions Second set 1-RM 30% to 10 repetitions	**10**
2nd	15	20 minutes Training: 60 seconds with 60% MHR Rest: 60 seconds with MHR 50%	First set: 1-RM 40% up to 10 repetitions Second set 1-RM 40% up to 10 repetitions Third set 1-RM 40% up to 10 repetitions	**10**
3rd	15	25 minutes Training: 60 seconds with 65% MHR Rest: 60 seconds with MHR 50%	First set: 1-RM 50% up to 10 repetitions Second set 1-RM 50% up to 10 repetitions Third set 1-RM 50% up to 10 repetitions	**10**
4th	15	25 minutes Training: 60 seconds with 65% MHR Rest: 60 seconds with MHR 55%	First set: 1-RM 55% up to 10 repetitions Second set 1-RM 55% up to 10 repetitions Third set 1-RM 55% up to 10 repetitions	**10**
5th	15	30 minutes Training: 60 seconds with 70% MHR Rest: 60 seconds with MHR 55%	First set: 1-RM 60% up to 10 repetitions Second set 1-RM 60% up to 10 repetitions Third set 1-RM 60% up to 10 repetitions	**10**
6th	15	30 minutes Training: 60 seconds with 70% MHR Rest: 60 seconds with MHR 55%	First set: 1-RM 65% up to 8 repetitions Second set 1-RM 65% up to 8 repetitions Third set 1-RM 65% up to 8 repetitions	**10**
7th	15	35 minutes Training: 60 seconds with 75% MHR Rest: 60 seconds with MHR 60%	First set: 1-RM 70% up to 8 repetitions Second set 1-RM 70% up to 8 repetitions Third set 1-RM 70% up to 8 repetitions	**10**
8th	15	35 minutes Training: 60 seconds with 75% MHR Rest: 60 seconds with MHR 60%	First set: 1-RM 75% up to 8 repetitions Second set 1-RM 75% up to 8 repetitions Third set 1-RM 75% up to 8 repetitions	**10**

Table 1: resistance and aerobic interval training protocol of the subjects

How to use nettle

First, nettle leaves were purchased from medicinal plants stores in Tabriz and then powdered using an electric grinder. During the intervention, patients used 100 mg/kg body weight of nettle hydroalcoholic extract dissolved in a glass of water after each main meal at the time of drug consumption prescribed by a physician (38).

Blood sampling

Subjects were drained of 5 cc of brachial vein in-vitro after 12 hours of fasting in the two pre-test stages and 48 hours after the last training session in the post-test stage. In the first step, according to the instructions provided for blood sampling conditions, the subjects were asked to avoid any strenuous physical activity, stressful conditions, and take supplements and medications one week before blood sampling. Blood samples were poured into tubes containing EDTA anticoagulant and centrifuged at 15,000 rpm for plasma separation for 15 minutes, frozen at -70 ° C and stored for subsequent analysis.

Measurement of biochemical variables

Serum levels of IL-33 were measured using ELISA method and Bioassay Technology Laboratory kit (Laboratory made in China) with sensitivity (2.12 ng / l). Serum glucose level measured by ELISA method using Pars kit made in Iran at a sensitivity of 5 mg/dL, and serum insulin levels were measured by ELISA using a Diaplus kit made in the United States at a sensitivity of 1 µU / L. The insulin resistance index formula was used to calculate insulin resistance.

HOMA-IR = (Glucose (mg / dl) × Insulin) / 405

Real time-PCR technique

Real time-PCR technique was used to evaluate changes in CTRP3 and IL-1β gene expression. For this purpose, RNA of blood samples was first extracted by TrizoL. RNA extraction of blood samples was performed using a kit (Bio Basic, L3r8t4, RNA Blood Jit Inc. Canada) according to the protocol of the country of manufacture. (24) (Table 2,3).

Statistical method

Shapiro-Wilk test was used to evaluate the normality of data distribution. After ensuring the normal distribution of data, to compare the mean scores of pre-test and post-test indices of experimental groups and control group of one-way analysis of variance and if significant Tukey post hoc test, for Differences between groups were used. All statistical analyzes were performed using SPSS software version 22 with a significance level ($p<0.05$).

Gene	Sequence of primer pairs	Amplification length
CTRP3 F	GAGTCTCCACAAACCGGAGG	**134 (bp)**
CTRP3 R	TCACCTTTGTCGCCCTTCTC	
IL-1 β F	TGATGGCTTATTACAGTGGCAATG	**140(bp)**
IL-1 β R	GTAGTGGTGGTCGGAGATTCG	
GAPDH F	ATCGTGCGTGACTTAAG	**87(bp)**
GAPDH R	GTCATCACCATTGGCAAT	

Table 2: Sequence of primers of studied genes

Product	Syber mix (µl)	primers (µl)	Taq polymerase (µl)	cDNA	DdH2O (µl)
CTRP3	12.5	0.5	0.15	2	**9**
IL-1 β	12.5	0.5	0.15	2	**9**
GAPDH	12.5	0.5	0.15	2	**9**

Table 3: PCR components for gene amplification

3. Results

The physiological characteristics of the subjects in the pre-test and post-test stages after 8 weeks of combined training are presented in Table 4. There were no significant differences in the levels of glucose, insulin, insulin resistance, IL-33, IL-1β and CTRP3 in the pretest stage and the groups were homogeneous. Also in the present study, glucose, insulin, insulin resistance, IL-33, IL-1β and CTRP3 indices and their changes in pre-test and post-test stages after 8 weeks of combined training were evaluated. Examination of the pre-test results of glucose, insulin, insulin resistance, CTRP3, IL-1β and IL-33 didn't show significant changes in the pre-test stage intergroup. In the post-test results, the results of analysis of variance showed that there was a significant difference between the glucose levels in the study groups after 8 weeks of intervention (P =0.001, F=34.39). Also, the results of Tukey post hoc test showed that glucose levels had a significant difference in the control group compared with Com group (p=0.001), the control group with NS group (p=0.001) and the control group with Com + NS group (p=0.001), but in the other groups it was not significant (p>0.05).

variable	group	Mean±SD	F	P
Age (years)	control	50.64±0.61	0.354	0.786
	Com	50.52±0.60		
	NS	50.69±0.61		
	Com+NS	50.74±0.62		
Height (cm)	control	158.74±0.78	0.988	0.405
	Com	159.17±0.67		
	NS	158.99±0.71		
	Com+NS	159.04±0.58		
Weight (kg)	control	80.41±2.94	2.262	0.091
	Com	78.85±3.83		
	NS	80.13±2.21		
	Com+NS	78.03±2.13		

BMI (kg / m2)	control	31.54±1.11	0.860	0.467
	Com	31.13±1.73		
	NS	31.82±1.27		
	Com+NS	31.74±0.90		
Glucose (mg / dl)	control	165.75±7.89	0.334	0.801
	Com	166.38±6.72		
	NS	168.28±8.36		
	Com+NS	167.11±5.83		

Table 4: Anthropometric and physiological characteristics of women with type 2 diabetes in research groups

Also, the results of the variance analysis showed that there was a significant difference between the values of insulin resistance in the study groups after 8 weeks of intervention (P = 0.001, F = 50.73). On the other hand, the results of Tukey post hoc test did show a significant difference in the values of insulin resistance in the control group compared with Com group (p=0.001), the control group with NS group (p= 0.001) and the control group with Com + NS group (p=0.001). but in the other groups it was not significant (p>0.05) (table 5).

Table 5: Results of one-way ANOVA statistical test to determine the differences in changes in research variables

Before: Pre-test values After: Post-test values

* ($p<0.05$)

		Control	Com	NS	Com+NS		
CTRP3	pre	235.60±3.30	236.67±3.75	235.66±2.68	235.41±2.84	0.482	0.696
	post	232.13±2.69	249.20±5.75	245.99±2.78	258.60±5.83	87.66	0.001*
IL-1β	pre	1.03±0.07	1.02±0.05	1.01±0.06	1.02±0.07	0.190	0.903
	post	1.02±0.06	0.68±0.04	0.70±0.05	0.65±0.06	139.23	0.001*
IL-33	pre	220.50±3.45	220.00±2.50	219.59±3.04	219.93±2.90	0.276	0.842
(ng/l)	post	220.30±2.73	242.40±4.10	238.11±2.85	241.63±4.08	131.44	0.001*
Glucose	pre	165.75±7.89	166.38±6.72	168.28±8.36	167.11±5.83	0.334	0.801
(mg/dl)	post	169.27±4.46	154.29±5.14	156.64±4.62	153.68±1.30	34.39	0.001*
HbA1C	pre	6.46±0.91	6.11±0.86	6.76±0.76	6.09±0.92	2.072	0.114
(%)	post	6.39±0.68	5.88±0.68	5.71±0.80	5.49±0.63	4.39	0.008*
Insulin	pre	11.04±0.96	11.04±0.96	10.98±0.85	10.96±0.79	0.036	0.991
(µIU/ml)	post	10.80±0.63	10.03±0.47	10.44±0.48	9.92±0.44	9.38	0.001*
HOMA-	pre	4.33±0.53	4.65±0.85	4.63±0.59	4.56±0.55	0.775	0.513
IR	post	4.46±0.63	2.45±0.74	2.51±0.46	2.08±0.43	50.73	0.001*

In the post-test results, the results of analysis of variance showed that there was a significant difference between insulin levels in the study groups after 8 weeks of intervention (P= 0.001, F= 9.38). Also, the results of Tukey post hoc test did show a significant difference in the insulin values of the control group compared with Com group (p =0.001), and the control group with the Com + NS group (p=0.001), but did not show a significant diffrence in the control group with the NS group (p=0.233) (table 6).

Group1	Group2	CTRP3	IL-1β	IL-33 (ng/l)	Glucose (mg/dl)	HbA1C (%)	Insulin (µIU/ml)	HOMA-IR
control	**Com**	0.001*	0.001*	0.001*	0.001*	0.214	0.001*	0.001*
control	**NS**	0.001*	0.001*	0.001*	0.001*	0.052	0.233	0.001*
control	**Com+NS**	0.001*	0.001*	0.001*	0.001*	0.005*	0.001*	0.001*
Com	**NS**	0.225	0.885	0.008*	0.548	0.907	0.136	0.994
Com	**Com+NS**	0.001*	0.430	0.933	0.985	0.434	0.924	0.297
NS	**Com+NS**	0.001*	0.122	0.039*	0.345	0.833	0.032	0.191

Table 6: Tukey post hoc test results of variables in research groups

*($p<0.05$)

On the other hand, the results of variance analysis showed that there was a significant difference between changes in IL-1β gene expression in the research groups after 8 weeks of intervention (P=0.001, F = 139.23). On the other hand, the results of Tukey post hoc test did show a significant difference in the expression of IL-1β gene in the control group compared with Com group (p=0.001), the control group with NS group (p=0.001) and the control group with Com + NS group (P=0.001) (figure 2).

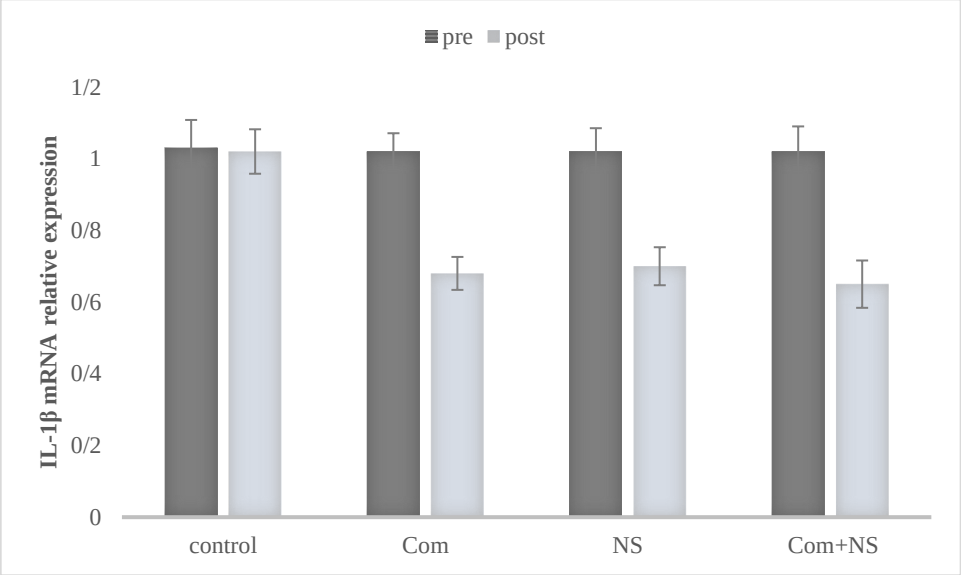

fig 2: IL-1β changes in groups, Com: combined training (resistance and aerobic interval training), NS: Nettle supplement, Com+NS: combined training + Nettle. The values represent means ± SEM, * Significant differences compared to the control group, $p<0.05$

Also, the results of variance analysis showed that there was a significant difference between IL-33 values in the research groups after 8 weeks of intervention (P = 0.001, F =131.44). On the other hand, the results of Tukey post hoc test did show a significant difference in the IL-33 values of the control group compared with Com group (p=0.001), the control group with NS group (p = 0.001) and the control group with Com + NS group (P = 0.001) (figure 3).

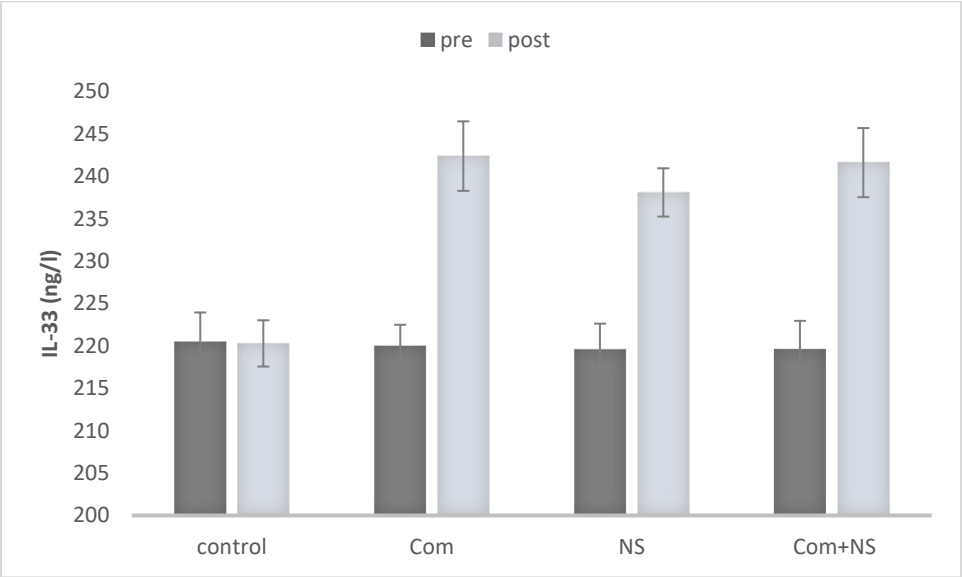

Fig 3: IL-33 changes in groups, Com: combined training (resistance and aerobic interval training), NS: Nettle supplement, Com+NS: combined training + Nettle. The values represent means ± SEM, * Significant differences compared to the control group, $p<0.05$

Also, the results of variance analysis showed that there was a significant difference between changes in CTRP3 gene expression in the study groups after 8 weeks of intervention (P =0.001, F = 87.66). On the other hand, the results of Tukey post hoc test did show a significant difference in the expression of CTRP3 gene in the control group compared with Com group (p=0.001), the control group with NS group (p=0.001) and the control group with Com + NS group (p=0.001) (figure 4).

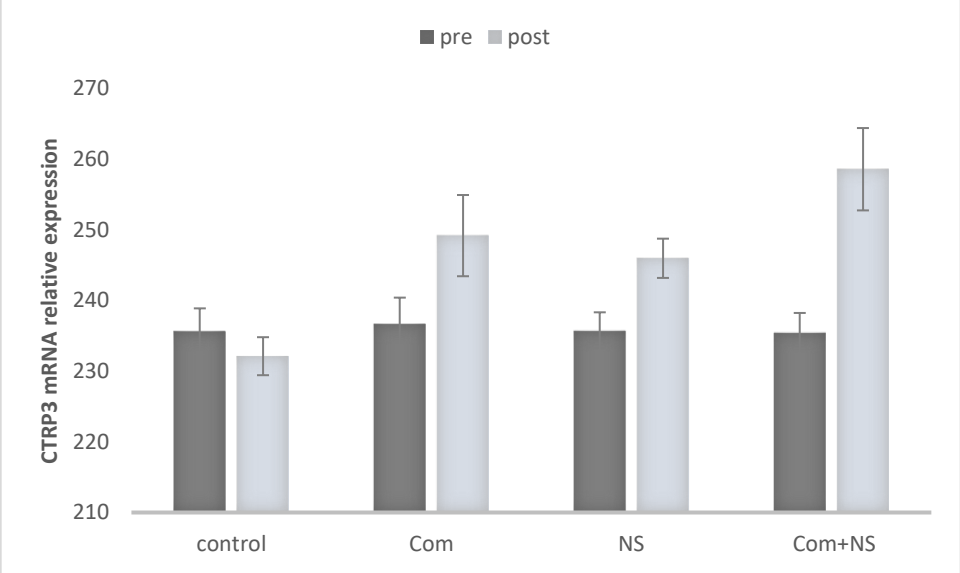

Fig 2: CTRP3 changes in groups, Com: combined training (resistance and aerobic interval training), NS: Nettle supplement, Com+NS: combined training + Nettle. The values represent means ± SEM, * Significant differences compared to the control group, $p<0.05$

4. Discussion

Exercise inherently increases insulin sensitivity and along with herbal supplements has been introduced as one of the most important options in the treatment and prevention of metabolic diseases and injuries. The aim of this study was to investigate the effect of 8 weeks of combined training with nettle supplementation on CTRP3, IL-1β gene expression and serum Levels of IL-33 in women with type 2 diabetes. The results of the present study showed that 8 weeks of combined training with nettle supplementation had a synergistic effect on a significant increase in CTRP3 and IL-33 expression compared to the pre-test. The results also showed a significant decrease in IL-1β and improvement in plasma glucose levels after 8 weeks of combined training with nettle supplementation in type 2 diabetic women. In fact, we saw a significant improvement in these factors in Com + NS group compared to other groups.

It has been suggested that training programs that improve body mass index (BMI) and reduce body fat can be involved in reducing inflammatory factors. In fact, training inhibits the release of inflammatory mediators, including IL1β from adipose tissue by reducing sympathy and increasing anti-inflammatory cytokines (25, 26). Findings of the study by Nasr-Esfahani et al., Which examined the effect of yoga training for eight weeks in women with type 2 diabetes, which is consistent with the results of the present study. Increased fat mass is one of the main reasons for insulin resistance, so reducing the amount of body fat mass can be expected to reduce insulin resistance and thus reduce inflammatory cytokine such as IL-1β, CRP (27). Martin et al. Also reported that 14 weeks of regular aerobic training significantly reduced IL-1β in obese mice (4).

The researchers said that exercise by positively regulating the Dual-specificity phosphatase (DUSP) family reduced inflammatory cytokine expression. This family is responsible for the dephosphorylation of phosphotyroine and phosphotyrosine, which are important residues in Mitogen-activated protein kinases (MAPK) that inactivate MAPK MAPKs play an important role as stimulants of IL-1β pro-inflammatory agents (28).

Another result of the present study is a increase in serum IL-33 levels following 8 weeks of combined training in type 2 diabetic women. Training seems to play a protective role against diabetes by inducing and increasing IL-33. Liu et al reported that combined aerobic and resistance training resulted in a significant increase in IL-33 and a significant decrease in glucose, insulin, and insulin resistance (29), which is consistent with the findings of the present study. Several mechanisms have been proposed regarding the protective role of IL-33 in obesity and diabetes. Research shows that the distribution of IL-33 in obese diabetic rats leads to a decrease in fat cells, a decrease in fasting glucose, and an improvement in insulin sensitivity (9). IL-33 has been shown to induce local accumulation of cells in the control of Th2 and cytokines in adipose tissue and also to polarize adipose tissue macrophages towards the active phenotype of the M2 variable, which is the function of IL-33 can play a role in controlling inflammation (9). In conclusion, IL-33 may play a protective role against obesity and diabetes by inducing Th2 cytokine and M2 anti-inflammatory macrophage in adipose tissue. Also, the results of the present study showed that 8 weeks of combined training (resistance and aerobic interval training) caused a significant increase in CTRP3 levels in type 2 diabetic women. Hasgawa et al. Showed that 8 weeks of regular aerobic exercise significantly increased serum CTRP3 levels along with a significant reduction in fat percentage in middle-aged men and women. In addition, research shows that aerobic training inhibits intracellular signaling, including the Akt / mTOR / S6K cascade pathway, by improving metabolism (30). CTRP3 inhibits inflammatory pathways induced by lipopolysaccharides, fatty acids, and TLR ligands in adipose tissue.

In the present study, the expression of CTRP3 and IL-33 was increased in NS group and Com group. But the highest increase was observed in Com + NS group. Also, the expression of IL-1β and plasma glucose in the nettle supplement group and the training + nettle supplement group showed a significant decrease, with the highest decrease being related to the training + nettle supplement group. Nettle can inhibit the production of cytokines by inhibiting the necrotic factor pathway (NF-kB). NF-kB is present in the cytoplasm in the form of an inactive complex when bound to the IkB-α inhibitory subunit, and phosphorylation of this inhibitory subunit causes its spatial deformation, release from the complex, and activation of NF-kB. As a result, NFk-B remains inactive. Thus, nettle inhibits this important pathway in the production of cytokines (20). Nettle also improves blood sugar in type 2 diabetes by acting on pancreatic beta cells and increasing insulin secretion (31, 32).

In the present study, the combination of combined training (resistance and aerobic interval training) with nettle supplementation with synergistic effects led to better improvement in glycemic control, blood glucose and finally, reduction of inflammation in type 2 diabetic women. Due to the fact that patients with type 2 diabetes are constantly prone to inflammation, the use of combined training (resistance and aerobic interval training) with nettle supplementation can improve the inflammatory condition.

Acknowledgements

The authors express their gratitude to the people who participated in this study and to their research staff.

Funding

This study did not have any funds.

Compliance with ethical standards

Conflict of interest None declared.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

Conceptualization: S.B.B, S.D.; Methodology: S.B.B, S.D.; Software: S.B.B, S.D.; Validation S.B.B, S.D.; Formal analysis:S.B.B, S.D.; Investigation: S.B.B, S.D.; Resources: S.B.B, S.D.; Data curation: S.B.B, S.D.; Writing - original draft: A.D., S.M.; Writing - review & editing: S.B.B, S.D.; Visualization: S.B.B, S.D.; Supervision: S.B.B, S.D.; Project administration: S.B.B, S.D; Funding acquisition: S.B.B, S.D.

References

1. Souza KL, Gurgul-Convey E, Elsner M, Lenzen S. Interaction between pro-inflammatory and anti-inflammatory cytokines in insulin-producing cells. J Endocrinol. 2008 Apr;197(1):139-50. doi: 10.1677/JOE-07-0638. PMID: 18372240.

2. Riyahi Malayeri S, Azadniya A, Rasaee M J. Effect of eight-week High intensity interval training nd resveratrol intake on serum adiponectin and resistin in type 2 diabetic rats. Ijdld 2019; 18 (1) :8-1. URL: http://ijdld.tums.ac.ir/article-1-5708-en.html.

3. Riyahi Malayeri S, Kaka Abdullah Shirazi S, Behdari R, mousavi Sadati K. Effect of 8-week Swimming training and garlic intake on serum ICAM and VCAM adhesion molecules in male obese rats. JSSU 2019; 26 (10): 867-878.URL: http://jssu.ssu.ac.ir/article-1-4695-en.html.

4. Martin-Cordero L, Garcia JJ, Giraldo E, De la Fuente M, Manso R, Ortega E. Influence of exercise on the circulating levels and macrophage production of IL-1beta and IFNgamma affected by metabolic syndrome: an obese Zucker rat experimental animal model. Eur J Appl Physiol. 2009 Nov;107(5):535-43. doi: 10.1007/s00421-009-1140-4. Epub 2009 Aug 18. PMID: 19688220.

5. Peiró C, Lorenzo Ó, Carraro R, Sánchez-Ferrer CF. IL-1β Inhibition in Cardiovascular Complications Associated to Diabetes Mellitus. Front Pharmacol. 2017 Jun 13;8:363. doi: 10.3389/fphar.2017.00363. PMID: 28659798; PMCID: PMC5468794.

6. van Asseldonk EJ, Stienstra R, Koenen TB, Joosten LA, Netea MG, Tack CJ. Treatment with Anakinra improves disposition index but not insulin sensitivity in nondiabetic subjects with the metabolic syndrome: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2011 Jul;96(7):2119-26. doi: 10.1210/jc.2010-2992. Epub 2011 Apr 20. PMID: 21508140.

7. Hosseini M, Ghasem Zadeh Khorasani N, Divkan B, Riyahi Malayeri S. Interactive Effect of High Intensity Interval Training with Vitamin E Consumption on the Serum Levels of Hsp70 and SOD in Male Wistar Rats. Iranian J Nutr Sci Food Technol 2019; 13 (4) :21-28URL: http://nsft.sbmu.ac.ir/article-1-2689-en.html.

8. Froozandeh, E., Tofighi, A., Tolouei Azar, J. The Effect of 8 Weeks of Resistance and Aerobic Interval Training on Levels of GLP-1, NRG-1 and IL-33 in Type 2 Diabetic Women. *Sport Physiology*, 2020; 12(46): 117-138. doi: 10.22089/spj.2019.7434.1913

9. Miller AM, Liew FY. The IL-33/ST2 pathway--A new therapeutic target in cardiovascular disease. Pharmacol Ther. 2011 Aug;131(2):179-86. doi: 10.1016/j.pharmthera.2011.02.005. Epub 2011 Feb 26. PMID: 21356240.

10. Takhti M, Riyahi Malayeri S, Behdari R. Comparison of two methods of concurrent training and ginger intake on visfatin and metabolic syndrome in overweight women. Razi Journal of Medical Sciences. 2020;27(9):98-111.

11. Miller AM, Asquith DL, Hueber AJ, Anderson LA, Holmes WM, McKenzie AN, Xu D, Sattar N, McInnes IB, Liew FY. Interleukin-33 induces protective effects in adipose tissue inflammation during obesity in mice. Circ Res. 2010 Sep 3;107(5):650-8. doi: 10.1161/CIRCRESAHA.110.218867. Epub 2010 Jul 15. PMID: 20634488; PMCID: PMC4254700.

12. Berg A, Scherer P. The Online version of this article, along with updated information and services, is located on the World Wide Web. Journal of the American Heart Association. 2005; 96:939-49.

13. Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. Curr Opin Lipidol. 2003 Dec;14(6):561-6. doi: 10.1097/00041433-200312000-00003. PMID: 14624132.

14. Peterson JM, Wei Z, Wong GW. C1q/TNF-related protein-3 (CTRP3), a novel adipokine that regulates hepatic glucose output. J Biol Chem. 2010 Dec 17;285(51):39691-701. doi: 10.1074/jbc.M110.180695. Epub 2010 Oct 15. PMID: 20952387; PMCID: PMC3000950.

15. Zhang J, Zhang B, Cheng Y, Xu J. Low serum CTRP3 levels are associated with nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus. Cytokine. 2018 Jun;106:131-135. doi: 10.1016/j.cyto.2017.10.023. Epub 2017 Nov 4. PMID: 29113741.

16. Komosinska-Vassev K, Olczyk P, Kuźnik-Trocha K, Jura-Półtorak A, Derkacz A, Purchałka M, Telega A, Olczyk K. Circulating C1q/TNF-Related Protein 3, Omentin-1 and NGAL in Obese Patients with Type 2 Diabetes During Insulin Therapy. J Clin Med. 2019 Jun 5;8(6):805. doi: 10.3390/jcm8060805. PMID: 31195747; PMCID: PMC6617185.

17. Khademi Z, Imani E, Heidary Khormizi M, Poordad Khodaei A, Sarneyzadeh M, Nikparvar M. A Study on The Variation of Medicinal Plants Used for Controlling Blood Sugar and Causes of Self – Medication by Patients Referred to Bandarabbas Diabetic Center. J Diabetes Nurs 2013; 1 (1) :12-20

18. darabi S, hasanvand A, nourollahi A. Effects of garlic extract, olive leaf extract, nettle extract on serum inflammatory markers hsCRP and IL-6 and TNF-α in rats with diabetes. cmja 2016; 6 (1) :1452-1460.

19. Genc Z, Yarat A, Tunali-Akbay T, Sener G, Cetinel S, Pisiriciler R, Caliskan-Ak E, Altıntas A, Demirci B. The effect of stinging nettle (Urtica dioica) seed oil on experimental colitis in rats. J Med Food. 2011 Dec;14(12):1554-61. doi: 10.1089/jmf.2011.0028. Epub 2011 Aug 23. PMID: 21861725.

20. arighat esfanjani A, Namazi N, Bahrami A, Ehteshami M. Effect of Hydroalcoholic extract of Nettle (Urtica Dioica) on Glycemic Index and Insulin Resistance Index in Type 2 Diabetic Patients. Iranian Journal of Endocrinology and Metabolism 2012; 13 (6) :561-568

21. Jafari, Z., Samani, S.A. & Jafari, M. Insights into the bioactive compounds and physico-chemical characteristics of the extracted oils from *Urtica dioica* and *Urtica pilulifera*. *SN Appl. Sci.* **2**, 416 (2020). https://doi.org/10.1007/s42452-020-2219-0

22. Ziaei R, Foshati S, Hadi A, Kermani MAH, Ghavami A, Clark CCT, Tarrahi MJ. The effect of nettle (Urtica dioica) supplementation on the glycemic control of patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Phytother Res. 2020 Feb;34(2):282-294. doi: 10.1002/ptr.6535. Epub 2019 Dec 4. PMID: 31802554.

23. Saeid DabaghMasoud NikbakhtGlycemic Control by Exercise and Urtica Dioica Supplements in Men With Type 2 Diabetes.Jundishapur J Chronic Dis Care.2016;5(1):e31745.https://doi.org/10.17795/jjcdc-31745.

24. Nikroo H, Hosseini SRA, Fathi M, Sardar MA, Khazaei M. The effect of aerobic, resistance, and combined training on PPAR-α, SIRT1 gene expression, and insulin resistance in high-fat diet-induced NAFLD male rats. Physiol Behav. 2020 Dec 1;227:113149. doi: 10.1016/j.physbeh.2020.113149. Epub 2020 Sep 2. PMID: 32888948.

25. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol (1985). 2005 Apr;98(4):1154-62. doi: 10.1152/japplphysiol.00164.2004. PMID: 15772055.

26. Trøseid M, Lappegård KT, Mollnes TE, Arnesen H, Seljeflot I. The effect of exercise on serum levels of interleukin-18 and components of the metabolic syndrome. Metab Syndr Relat Disord. 2009 Dec;7(6):579-84. doi: 10.1089/met.2009.0003. PMID: 19900154.

27. Nasr Esfahani N, Taghian F. Effect of Eight Weeks of Yoga Training and Zinc Supplementation on the Levels of Interleukin-1 and C-reactive Protein in Women with Type II Diabetes. J Diabetes Nurs 2018; 6 (1) :374-385.

28. Chen HF, Chuang HC, Tan TH. Regulation of Dual-Specificity Phosphatase (DUSP) Ubiquitination and Protein Stability. Int J Mol Sci. 2019 May 30;20(11):2668. doi: 10.3390/ijms20112668. PMID: 31151270; PMCID: PMC6600639.

29. Liu Y, Liu SX, Cai Y, Xie KL, Zhang WL, Zheng F. Effects of combined aerobic and resistance training on the glycolipid metabolism and inflammation levels in type 2 diabetes mellitus. J Phys Ther Sci. 2015 Jul;27(7):2365-71. doi: 10.1589/jpts.27.2365. Epub 2015 Jul 22. PMID: 26311110; PMCID: PMC4540883.

30. Dadvar, N., Ghalavand, A., Zakerkish, M., Hojat, S., Alijani, E., Mahmoodkhanikooshkaki, R. The Effect of Aerobic Training and Urtica Dioica on Lipid Profile and Fasting Blood Glucose in Middle Age Female with Type II Diabetes. *Jundishapur Scientific Medical Journal*, 2017; 15(6): 507-516.

31. Dadvar N, Ghalavand A, Zakerkish M, Hojat S, Alijani E, Mahmoodkhanikooshkaki R. The effect of aerobic training and Urtica Dioica on lipid profile and fasting blood glucose in middle age female with type II diabetes. Jundishapur Scientific Medical Journal. 2017;15(6):507-16.

32. Hosseinpour Delavar, S., Boyerahmadi, A., Soleymani, A., Ghalavand, A. Effect of eight weeks of aerobic interval training and urtica dioica supplement on some inflammatory indicators and glycemic control in men with type 2 diabetes. *Jundishapur Scientific Medical Journal*, 2020; 19(2): 123-135. doi: 10.22118/jsmj.2020.200813.1814