Serum Tumor Necrosis Alpha Response to aerobic Exercise Versus Added Sugar Elimination in Obese Sedentary Females

Zainab S. Aly[1], Amr M. Elalfy[2], Yasmine M. Eletreby[3], Mohamed E. Khedr[4], Joseph W. Saweres[5], Reem Hamdy Abdelhady[6], Rasha Galal Elsafty[7], Amera S. Aly Yousef[8], Saleh M. Aloraini[9], Nevein N. Elagamy[10]

[1] Physical Therapy Lecturer, Department of Internal Medicine and Geriatrics, PhD, Horus University, New Damietta, Egypt. ORCID: 0009-0006-8597-4868. zaly@horus.edu.eg

[2] Lecturer of Physical Therapy for Burn and General Surgery, Faculty of Physical Therapy, Heliopolis University, Cairo, Egypt. amr.imam@hu.edu.eg

[3] Lecturer of Physical Therapy for Pediatrics and its Surgery, PhD, Faculty of Physical Therapy, Horus University, New Damietta, Egypt. yeletreby@horus.edu.eg

[4] Lecturer of Physical Therapy for Pediatrics and its Surgery, PhD, Faculty of Physical Therapy, Horus University, New Damietta, Egypt. memadeldin@horus.edu.eg

[5] Lecturer of Physical Therapy, Basic Science and Biomechanics Department, PhD, Faculty of Physical Therapy, Suez Canal University, Egypt. josephwageeh@pt.suez.edu.eg

[6] Department of Physical Therapy for Woman's Health, Faculty of Physical Therapy, Sinai University Kantara, Egypt, Reem.hamdy478@gmail.com | ORCID: 0000-0003-2826-3826

[7] Lecturer, Chest Diseases, Faculty of Medicine, Tanta University, Egypt. Rasha.elsafty@med.tanta.edu.eg | ORCID: 0000-0003-3194-295X

[8] Lecturer, Department of Physical Therapy for Cardiovascular, Respiratory Disorders and Geriatrics, Faculty of Physical Therapy, Alsalam University, Tanta, Egypt. Amira.Soliman@sue.edu.eg; amerayounes25@gmail.com

[9] Department of Physical Therapy, College of Applied Medical Sciences, Qassim University, Buraydah, Saudi Arabia. saloraini@qu.edu.sa | ORCID: 0000-0001-7939-8098

[10] Physical Therapy Lecturer, Department of Internal Medicine and Geriatrics, PhD, Horus University, New Damietta, Egypt. nnabil@horus.edu.eg

Abstract

Background: The transition of inflammatory response from short- to long-lived initiates a state of systemic lowgrade inflammation that breaks down the immune homeostasis leading to alterations all over the body, interrupting normal cellular physiology and raises most of non-communicable disease risks. Physical inactivity combined with obesity as the most common side effect, contributes greatly to the development of cardiovascular and arterial stiffening diseases on basis of aggravating inflammatory and oxidative stress responses. Both aerobic exercise and dietary sugar restriction are known interventions attempting to lower these risks counteracting for the disease progression through inhibiting the systemic low grade inflammatory state.

Aims: To evaluate the effects of 8-weeks of aerobic exercise program and added sugar elimination on body's inflammatory state in sedentary obese females aged 40–60 year.

Methods and results: 60 participants were randomly assigned to one of three groups considering 20 for each: group I (aerobic exercise), group II (added sugar elimination), group III (aerobic exercise combined with added sugar elimination). TNF alpha levels and subject's score on the inflammatory questionnaire were measured pre- and post-intervention. All groups showed significant improvement in TNF alpha levels and inflammatory questionnaire scores, with the combined group showing the greatest improvement (36.060%, 30.329% respectively).

Conclusion: Both aerobic exercise and added sugar elimination independently or synergistically enhance the body's anti-inflammatory mechanisms in sedentary obese females.

Keywords: aerobic exercise, added sugar, systemic low-grade inflammation, TNF alpha, obesity

1. Introduction

Physical inactivity as a high risk factor for cardiovascular disease impairs the active role of exercise in enhancing cardiovascular metabolism and function, reducing oxidative stress and chronic inflammation, regulating insulin sensitivity and autophagy, and increasing myocardial mitochondrial efficiency **(1).**

Physical exercise is the main determinant of a subject′s functional performance and healthy aging. It enhances antioxidant response by reducing inflammatory and oxidative stress damage signalling alongside with increasing antioxidant enzymes and nitric oxide levels. It can also decrease pro-inflammatory signals and improve vascular endothelial function **(2).**

Physical exercise exibits a preventive and treating tool for almost all disease measures. It reduces inflammation by regulating the effect of pro-inflammatory toll-like receptors (TLRs) on innate immune cells after exercise, together with shielding against insulin resistance and metabolic disease risks **(3).**

Added sugars and processed foods are key factors in both the triggering and aggravation of inflammation, which is strongly linked to the development of obesity, T2D, metabolic syndrome and cardiovascular insufficiency **(4).**

Physical activity increases T-regulatory cell levels, decreases immunoglobulin secretion and shifts the Th1/Th2 balance to a decreased Th1 cell production. Moreover, it also promotes the release of IL-6 from muscles as a myokine with an anti-inflammatory response through IL-10 secretion and IL-1β inhibition **(5).**

Risky added sugar consumption with its modulation of microbiota, promotes systemic (low grade) inflammation in consistence with metabolic dysregulation and endotoxemia **(6).**

According to the lipotoxicity theory, increased liver FFA synthesis in response to dietary sugar consumption generates more FFA metabolites that is involved in triggering inflammatoryand oxidative stress reactions **(7).**

TNF-α has a great impact on healthy metabolism and metabolic diseases, particularly, obesity-linked glucose metabolism and insulin resistance (IR). High TNF-α levels corresponds strongly to obesity and low-grade chronic inflammatory status as well as to the possibly derived cardiometabolic disorders **(8).**

Purpose of The Study

To assess the serum tumour necrosis alpha and inflammatory reaction to aerobic exercise in comparison with added sugar elimination.

2. Methods

2.1. Study design:

60 sedentary obese female aged 40 to 60 with high normal TNF-alpha levels and some symptoms of systemic inflammation (>75 score on the inflammatory questionnaire) were incorporated in three groups, 20 patients for each. All patients were diagnosed as having high normal TNF-alpha levels and some symptoms of systemic inflammation (>75 score on the inflammatory questionnaire).

.

2.2. Sampling strategy: any sedentary obese 40-60 years old female with BMI of 30-40 diagnosed as having a high normal or mildly elevated TNF- alpha levels with symptoms of systemic inflammation (>75 score on the inflammatory questionnaire) and had none of the exclusion criteria could be included in this study. Patients with orthopaedic or cardiac disorders those that could interfere with their ability to walk or exercise, were altogether excluded .

2.3. Instrumentation: computerized treadmill, sphygmomanometer, weight and height scale, kits and tubes of blood samples.

2.4. Evaluational approach: Subjects were randomly incorporated into three groups (20 female for each): group I accomplished a uniform programme of aerobic exercise, group II accomplished a special programme of added sugar elimination, group III accomplished the same programme of aerobic exercise combined with the same programme of added sugar elimination.

2.5. Measurements:

Initial evaluation: in form of estimation of the serum TNF- alpha levels and the subject′s score on the inflammatory questionnaire.

Final evaluation: applied at the end of the study (8 weeks after the initial evaluation) and in the same form and sequence (estimation of the serum TNF- alpha levels and the subject′s score on the inflammatory questionnaire)

2.6. Intervention:

1. Group I performed a specialized programme of aerobic exercise with these prescriptions.

- Frequency: 3-5 times /week along the whole study period.
- Intensity: 65-70% of the maximal heart rate (220- age x 60/100).
- Duration: 50 min including:
  10 min warming up in the form of exercise movements (stretching and flexibility) in standing position.
  30 min active phase (walking on a treadmill).

10 min cooling down in the form of exercise movements (stretching and flexibility) performed in the seated position.

2. Group II performed prescribed programme of added sugar elimination.
3. Group III performed the same programme of aerobic exercise combined with the same programme of added sugar elimination.

3. Results

Table (1): Comparisons of the three groups at baseline

Parameter	Group I		Group II		Group III		All participants		Sig.
	Median	Q1-Q3	Median	Q1-Q3	Median	Q1-Q3	Median	Q1-Q3	
Age (years)	49.5	45.3-53	47	43.3-50	47	41-52.8	48	43-52	.527
BMI (kg/m^2)	36.7	35.9-39.4	39.3	37.3-39.5	36.7	35.9-39.1	38.6	36.1-39.5	.062
TNF	38.5	36-42.8	44	39-53	44	37-54	43	37-48.8	.037
Questionnaire score	99.5	92.8-112.8	113.5	100.8-117.8	121	109-127.8	112	100-119.8	<.001

Notes: Q1-Q3 = 25th – 75th percentiles. Sig. = statistical significance (p-value). The test of significance is KruskalWallis H-test.

Table (1) shows no statistically significant difference in age and BMI between the three groups at baseline. The level of TNF was higher in groups II and III vs. group I at baseline (figure 1). The questionnaire score was higher in groups III>II>I at baseline (figure 2).

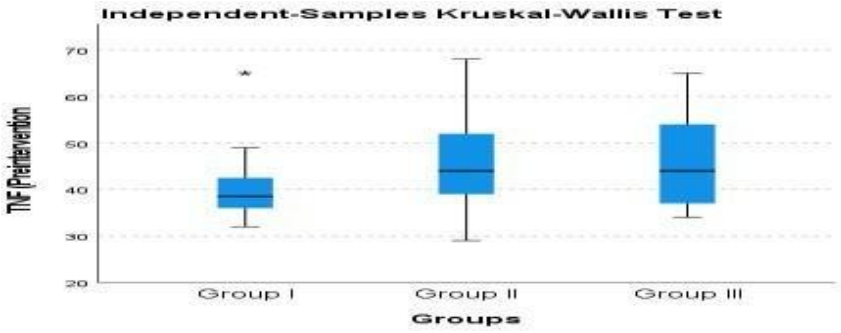


Figure (1): Baseline TNF

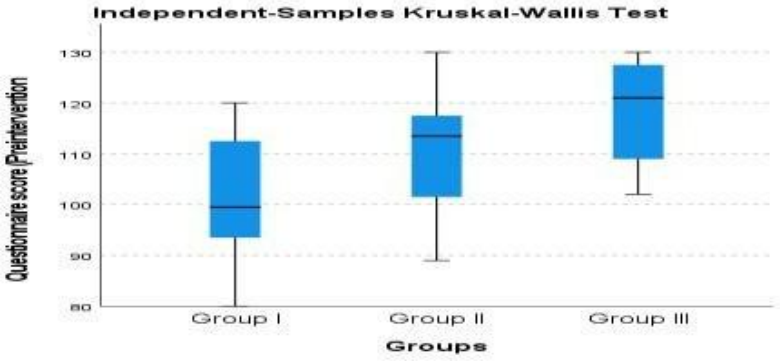


Figure (2): Baseline questionnaire score

Table (2): Correlations of TNF level change (preintervention-postintervention) with study parameters

Parameter	Group I		Group II		Group III		All participants	
	r_s	Sig.	r_s	Sig.	r_s	Sig.	r_s	Sig.
Age (years)	-.169	.477	.211	.371	.030	.900	-.034	.795
BMI (kg/m^2)	-.108	.651	.102	.669	.186	.432	.109	.408
Questionnaire score change	.419	.066	-.044	.853	.409	.073	.137	.297

Notes: r_s = Spearman's correlation coefficient. Sig. = statistical significance (p-value).

Table (2) shows no statistically significant correlation between TNF change vs. age, BMI, and questionnaire score change. However, the correlation between TNF and questionnaire score changes in groups I and III was of medium strength with marginal significance (p<.1 but>.05).

Table (3): Postintervention TNF level adjusted to preintervention values

Group	Unadjusted		Adjusted		F	Sig.	Partial η^2
	Mean	SD	Mean	SE			
Group I	**28.70**	**4.256**	**30.233**	**.723**	**2.982**	**.059**	**.096**
Group II	**30.80**	**5.845**	**29.830**	**.710**			
Group III	**28.50**	**4.059**	**27.937**	**.705**			

Notes: SD = standard deviation. SE = standard error. Sig. = statistical significance (p-value). Partial Eta squared is a measure of effect size. The test of significance is the one-way analysis of covariance (ANCOVA).

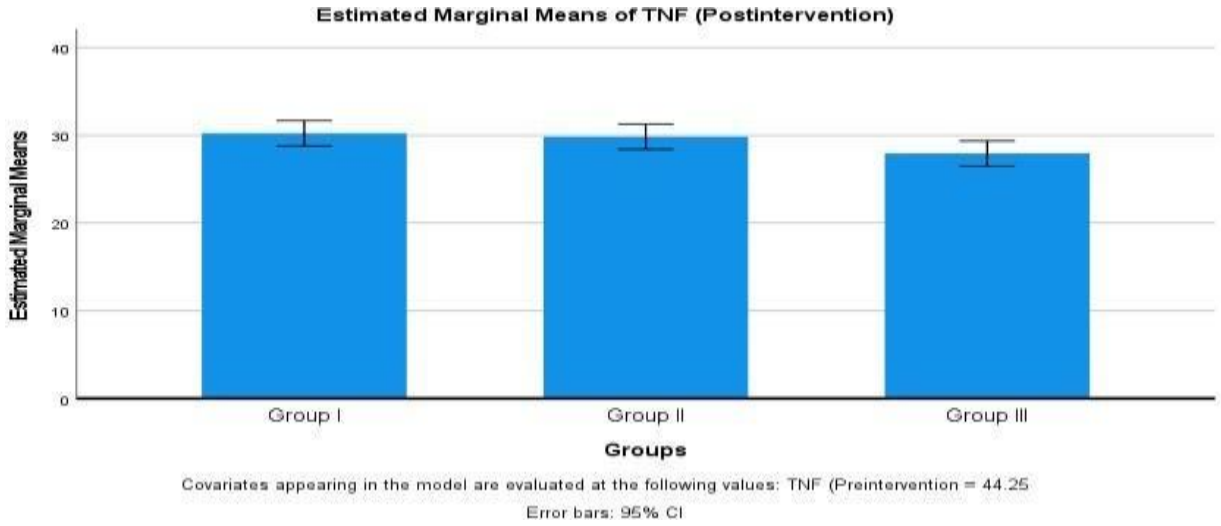


Figure (3): Postintervention TNF level adjusted to preintervention values

Table 3 and Figure 3 show a higher adjusted mean TNF level in group I>group II>group III which was marginally significant.

Table (4): Postintervention questionnaire score adjusted to preintervention values

Group	Unadjusted		Adjusted		F	Sig.	Partial η^2
	Mean	SD	Mean	SE			
Group I	**82.35**	**9.538**	**90.070**	**1.454**	**58.445**	**<.001**	**.676**
Group II	**97.00**	**10.603**	**96.778**	**1.310**			
Group III	**83.25**	**12.949**	**75.752**	**1.446**			

Notes: SD = standard deviation. SE = standard error. Sig. = statistical significance (p-value). Partial Eta squared is a measure of effect size. The test of significance is the one-way analysis of covariance (ANCOVA).

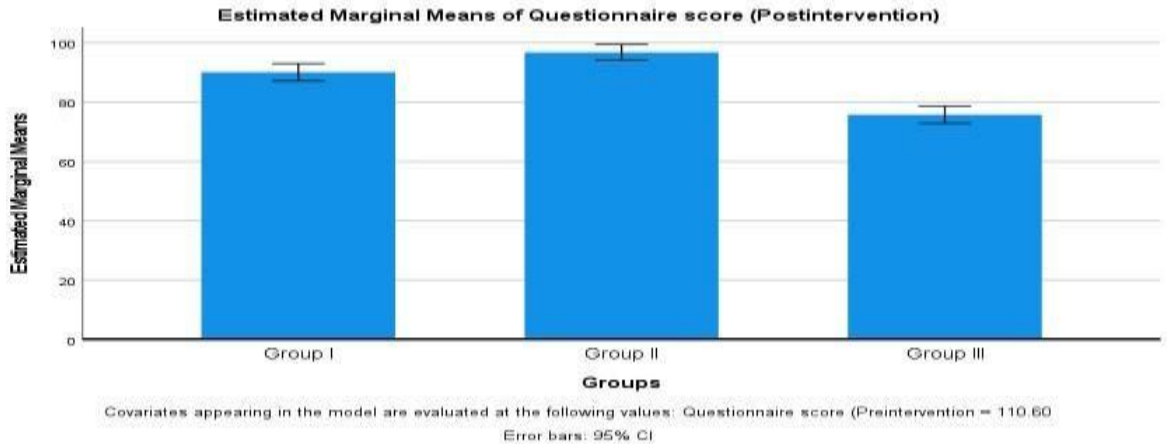


Figure (4): Postintervention questionnaire score adjusted to preintervention values

Table 4 and Figure 4 show a higher adjusted mean questionnaire score in group II>group I>group III which was statistically significant.

Table (5): Percentage of improvement in TNF and questionnaire score in the three groups

Parameter	Group I		Group II		Group III		Sig.	$\square_2$
	Mean	SD	Mean	SD	Mean	SD		
TNF level	28.153	7.9714	33.126	7.2247	36.060	10.9142	.022	.125
Questionnaire score	19.044	4.3296	12.530	4.2226	30.329	6.8619	<.001	.671

Notes: SD = standard deviation. Sig. = statistical significance (p-value). Eta squared ($\square^2$) is a measure of effect size, which is considered small, medium, or large if eta squared equals 0.01, 0.06, or 0.14, respectively. The test of significance is one-way ANOVA.

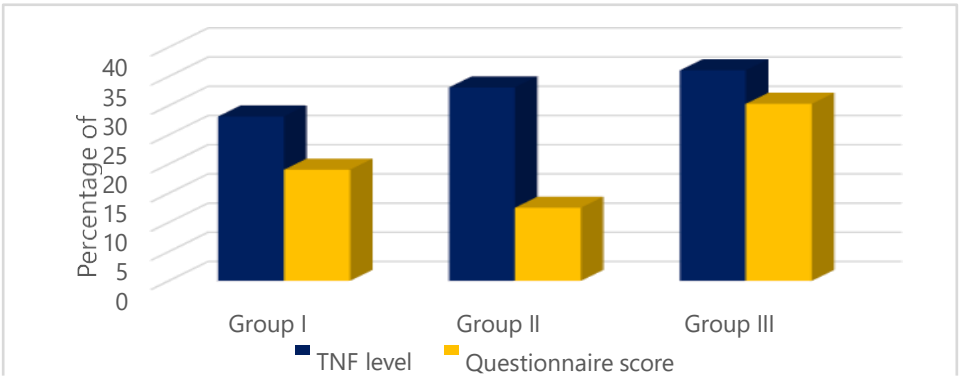


Figure (5): Percentage of improvement in TNF and questionnaire score in the three groups

Table (5) and figure (5) showed a statistically significant difference in the percentage of improvement in TNF level with medium effect size, and in questionnaire score with large effect size. Post-hoc Tukey's tests revealed a significantly higher improvement of TNF in group III>group I, and a significantly higher improvement of questionnaire score in group III>group I>group II.

Statistical analysis:

IBM-SPSS software, which was released by IBM Corp. in 2020, was used to enter andanalyse data. IBM Corp., Armonk, NY; IBM SPSS Statistics for Windows, Version 27.0. Shapiro-Wilk's test (normally distributed data has p>0.050) and Q-Q-plots were used to first check the quantitative data for normality. Examining boxplots allowed for the detection of notable outliers. The mean, standard deviation, median, and Q1 (25th percentile) through Q3

(75th percentile) were used to express the quantitative data. To compare numerical data across several groups, the one-way ANOVA and its nonparametric counterpart, the Kruskal-Wallis H-test, were employed. After adjusting for a covariate variable, a numerical variable was compared between groups using one-way ANCOVA. The direction and strength of the relationship between two numerical variables were evaluated using Spearman's correlation test. Results were deemed statistically significant for any test if the p-value was less than or equal to 0.050. When necessary, the data were graphically presented using the appropriate charts.

4. Discussion

The study at hand revealed a significant improvement in the subject's TNF alpha levels in response to aerobic exercise, added sugar elimination and when combining both of them with a percentage of (28.153 %, 33.126%, 36.060%) respectively, and a significant improvement in the subject's inflammatory symptoms with a percentage of (19.044%, 12.530%, 30.329% respectively) according to their scores on the inflammatory questionnaire. This comes in support with **(9)** when he examined , through a systematic review, the exercise′s anti-inflammatory effect. Regular exercise therapies have been shown to lower the inflammatory markers such as IL 6, TNF α, and C-reactive protein.

And goes hand in hand with **(10)** when he examined the effects of acute aerobic exercise on different cytokines and recorded an elevation in serum klotho levels and a reduction in IL1β, TNF-α levels, which all support the acute anti-inflammatory effect of exercise in RA patients.

This is also emphasized by the results of the systematic review comparing the anti-inflammatory effect of exercise alone or combined with caloric restriction suggesting better anti-inflammatory effect (larger reduction in TNF-α and IL-6, reduction in CRP) of combining exercise and calroic restriction than being separated **(11).**

These results come in consistence with **(12)** in the systematic review of evaluating the impact of ten various sources of food on different biomarkers of inflammation. It was concluded that added nutritive sweeteners increased TNF-α levels, which is also supported by **(13)** as he stated that body′s response to high dietary sugars signals inflammatory changes and impaired integrity in addition to metabolic endotoxemia and hepatic steatosis. The results also align with **(14)** when he investigated how aerobic interval workouts affected the ratio between interleukin-10 and tumor necrosis factor considering the levels of adipokines in multiple – sclerotic females. It was concluded that tumor necrosis factor α levels dropped dramatically after the aerobic interval workouts.

Saffouri GB (15), with his pilot interventional study about shifting from a diet with minimal fiber content to excessive simple sugar regimen , demonstrated: a significant triggering of functional gastrointestinal disorders , a decline in small intestinal diversity of microbes and a raise of small intestinal permeability which is widely known as a trigger of immunological response contributing to intestinal and systemic inflammation.

The results also come in accordance with **(16)** when he suggested through his study that the intake of simple sugars which is linked to many non-communicable diseases predisposes to inflammatory cascades and colitis via pathogenic alteration of gut microbiota in mice.

(17) also stated that high Simple Sugar diets trigger a Pro-Inflammatory Response via Gut Microbiota modulation and TLR4 Signaling. As it significantly enhanced neutrophil infiltration while raising the levels of IL-6, IL-1β, and TNF-α, which all support its dramatic role in disturbing barrier integrity and systemic immune reactions.

Conclusion

To wrap it up, both aerobic exercise and added sugar elimination can significantly lower the TNF- Alpha levels and systemic inflammatory potentials in sedentary obese females, whether implemented independently or in combination.

References

[1] Wang B, Gan L, Deng Y, Zhu S, Li G, Nasser MI, Liu N, Zhu P. Cardiovascular Disease and Exercise: From Molecular Mechanisms to Clinical Applications. J Clin Med. 2023; 12(6):2143.

[2] El Assar M, Álvarez-Bustos A, Sosa P, Angulo J, Rodríguez-Mañas L. Effect of Physical Activity/Exercise on Oxidative Stress and Inflammation in Muscle and Vascular Aging. Int. J. Mol. Sci. 2022; 23: 8713.

[3] Collao N, Rada I, Francaux M, Deldicque L, Zbinden-Foncea H. Anti-Inflammatory Effect of Exercise Mediated by Toll-Like Receptor Regulation in Innate Immune Cells – A Review: Anti-inflammatory effect of exercise mediated by Toll-like receptor regulation in innate immune cells. International Reviews of Immunology. 2019; 39(2): 39–52.

[4] Ma X, Nan F, Liang H, Shu P, Fan X, Song X, Hou Y, Zhang D. Excessive intake of sugar: An accomplice of inflammation. Front Immunol. 2022; 13:988481.

[5] Sharif K, Watad A, Nicola, Bragazzi L, Lichtbroun M, Amital H, Shoenfeld Y. Physical activity and autoimmune diseases: Get moving and manage the disease. Autoimmunity Reviews. 2018; 17(1): 53-72.

[6] Satokari R. High Intake of Sugar and the Balance between Pro- and Anti-Inflammatory Gut Bacteria. 2020 ;12(5):1348.
[7] Hodson L, Gunn PJ. The regulation of hepatic fatty acid synthesis and partitioning: the effect of nutritional state. Nat Rev Endocrinol. 2020; 15:689–700.
[8] Galvez I, Navarro MC, Martin-Cordero L, Otero E, Hinchado MD, Ortega E. The Influence of Obesity andWeight Loss on the Bioregulation of Innate/Inflammatory Responses: Macrophages and Immunometabolism. Nutrients. 2022; 14:612.
[9] Beibei Luo a b †, Dao Xiang c d †, Xiaorong Ji a, Xuan Chen a, Rui Li a, Shuxin Zhang a, Yujun Meng a, David C. Nieman e, Peijie Chen a f. The anti-inflammatory effects of exercise on autoimmune diseases: A 20-year systematic review. Journal of Sport and Health Science. 2024; 13 (3):353-367.
[10] Ercan Z, Deniz G, Yentur SB, Arikan FB, Karatas A, Alkan G, Koca SS. Effects of acute aerobic exercise on cytokines, klotho, irisin, and vascular endothelial growth factor responses in rheumatoid arthritis patients. Ir J Med Sci. 2023; 192(1):491-497.
[11] Khalafi M, Symonds M. E, Akbari A. The impact of exercise training versus caloric restriction on inflammation markers: a systemic review and meta-analysis. Critical Reviews in Food Science and Nutrition. 2022; 62(15): 4226–4241.
[12] Qi XY, Chiavaroli L, Lee D, et al. Effect of Important Food Sources of Fructose-Containing Sugars on Biomarkers of Inflammation: A Systematic Review and Meta-Analysis of Controlled Trials. Current Developments in Nutrition. 2021; 5(2): 1083.
[13] Do MH, Lee E, Oh MJ, Kim Y, Park HY. High-glucose or -fructose diet cause changes of the gut microbiota and metabolic disorders in mice without body weight change. Nutrients. 2018;10:761.
[14] Mokhtarzade M , Ranjbar R , Majdinasab N , Patel D , Shamsi MM. Effect of aerobic interval training on serum IL-10, TNFα, and adipokines levels in women with multiple sclerosis: possible relations with fatigue and quality of life. Endocrine. 2017; 57(2):262-271.
[15] Saffouri GB, Shields-Cutler RR, Chen J, Yang Y, Lekatz HR, Hale VL, Cho JM, Battaglioli EJ, Bhattarai Y, Thompson KJ, et al. Small intestinal microbial dysbiosis underlies symptoms associated with functional gastrointestinal disorders. Nat. Commun. 2019;10:2012.
[16] Khan S, Waliullah S, Godfrey V, Khan MAW, Ramachandran RA, Cantarel BL, Behrendt C, Peng L, Hooper LV, Zaki H. Dietary simple sugars alter microbial ecology in the gut and promote colitis in mice. Sci Transl Med. 2020 Oct 28;12(567):eaay6218.
[17] Fajstova A, Galanova N, Coufal S, Malkova J, Kostovcik M, Cermakova M, Pelantova H, Kuzma M, Sediva B,
Hudcovic T, Hrncir T, Tlaskalova-Hogenova H, Kverka M, Kostovcikova K. Diet Rich in Simple Sugars Promotes Pro-Inflammatory Response via Gut Microbiota Alteration and TLR4 Signaling. Cells. 2020; 9(12):2701.