

The effect of fasting and physical exercise on serum levels of selected cytokines in middle - aged individuals - pilot study

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Abstract:

Background and Study Aim: In the era of global health and social threats, Innovative Agonology offers a unique approach to sustainable psychosocial development also referring to the threats of civilization diseases. Fasting and physical exercise are known to modulate immune functions, including the production and release of cytokines—key signaling molecules involved in regulating inflammatory processes. However, there are limited data on the combined effects of fasting and physical exercise on cytokines profile in humans. The aim of this study was to determine the effect of an 8-day fasting and physical exercise on the concentrations of selected proinflammatory and anti-inflammatory cytokines in the serum of adults.

Material and Methods: The experiment involved 6 middle-aged individuals (4 men, 2 women) who practice yoga, martial arts and strength training as amateurs. Qualified participants fasted for 8 days. Blood samples were collected before and after physical exercise – both before and after the end of the fast. The determination of 27 cytokines was performed using the Bio-Plex Pro Human Inflammation Assays platform (Bio-Rad).

Results: The results showed a statistically significant increase in IL-8 concentration only after 8 days of fasting and immediately after the end of physical exercise. Fasting caused a significant increase in MIP-1β concentration only 1 hour after the end of the exercise test. In the case of the remaining cytokines tested, no statistically significant changes in response to the interventions were demonstrated.

Conclusions: The obtained data suggest that fasting and physical exercise can selectively modulate the immune response, particularly by affecting cytokines involved in leukocyte recruitment. These results may have important implications for understanding physiological mechanisms of adaptation under metabolic stress conditions and in the context of nutritional and exercise interventions.

Keywords: innovative agonology, immune functions, physical exercise, metabolic stress,

Dictionary:

Cytokines – are low molecular weight proteins that play a key role in regulating the immune and inflammatory response, as well as in communication between cells of the immune, nervous and endocrine systems [4,5].

Innovative Agonology – is an applied science dedicated to promotion, prevention, and therapy related to all dimensions of health and the optimization of activities that increase the ability to survive (from micro to macro scales) [1].

1. Introduction

Innovative Agonology (INNOAGON) is an applied science dealing with promotion, prevention and therapy in relation to all dimensions of health. It is an interdisciplinary science combining combat theory, praxeology and modern knowledge in the field of exercise physiology [1]. In the era of global health and social threats, INNOAGON offers a unique approach to sustainable psychosocial development also referring to the threats of civilization diseases [2,3]. More and more often, in society, there are proposals for cleansing diets, fasting, or so-called fasts, which are supposed to lead to improved immunity of the body.

Cytokines are low molecular weight proteins that play a key role in regulating the immune and inflammatory response, as well as in communication between cells of the immune, nervous and endocrine systems [4,5]. Their concentration changes dynamically in response to various physiological stressors, such as fasting (F) or physical exercise (PhE). Disturbances in their expression and regulation can lead to the development of many chronic diseases, including metabolic syndrome, type 2 diabetes and cardiovascular diseases [6,7].

PhE, especially high-intensity exercise, leads to a temporary increase in the concentration of proinflammatory cytokines, such as interleukin 6 (IL-6), interleukin 8 (IL-8) and tumor necrosis factor alpha (TNF- α), as well as anti-inflammatory cytokines, such as interleukin 10 (IL-10) or interleukin 1Ra (IL-1Ra) [8-10]. IL-6, one of the best-known myokines, can increase in serum in response to exercise lasting more than 2 hours, which reflects its role not only in regulating the inflammatory response but also in glucose and lipid metabolism [11,12]. IL-8 is a chemokine with chemotactic properties, especially for neutrophils. Its increase after intense exercise may be important in the recruitment of immune cells to muscle microinjuries [13]. Macrophage inflammatory protein 1 beta (MIP-1 β) is another chemokine from the CC group, which is involved in attracting monocytes, lymphocytes and NK cells. Studies have shown that its expression can increase both after exercise and in conditions of caloric restriction or F [14,15]. The inflammatory response may also depend on the time elapsed since the end of PhE. It has been shown that the levels of some cytokines, e.g. IL-10, increase 1 hour after the end of activity, which may indicate a later phase of the anti-inflammatory exercise response [16].

The state of F, both short-term and long-term, affects the cytokine profile. Energy restriction usually leads to a decrease in immune activity, but some cytokines, including IL-6 and MIP-1 β , may increase, probably as an adaptive response to metabolic stress [17-19]. Studies by Schneider et al. [20] have shown that after 8 days of F, IL-6 and TNF- α levels increase, which may reflect the mobilization of the body to obtain energy from alternative sources.

Despite numerous studies analyzing the effect of PhE on the concentration of individual cytokines, there is a limited number of scientific studies evaluating the simultaneous effect of F and PhE on the cytokine profile, especially in the middle-aged population. Understanding these interactions may provide valuable information on the body's adaptive mechanisms in response to metabolic and physical stressors. In addition, studies on middle-aged people are particularly important because with age, low-grade inflammatory processes ("inflammaging") increase, which may modulate the body's response to PhE or F [21,22]. Understanding the cytokine profile in this group may be important for the prevention of lifestyle diseases associated with diet and PhE.

The aim of this study is to assess the effect of F and PhE on the concentration of selected proinflammatory and anti-inflammatory cytokines in serum in middle-aged people. Analysis of these parameters will allow for a better understanding of the mechanisms of the immune response under conditions of metabolic and physical stress and may contribute to the development of intervention strategies to improve the health of this population group.

2. Materials and Methods

Study participants and ethical considerations

This study included 6 middle-aged individuals, consisting of 4 males and 2 females who practice yoga, martial arts and strength training as amateurs, with average characteristics as follows: age 55.33 ± 11.24 years, height 175.50 ± 6.47 cm, and body mass 77.30 ± 16.26 kg. Participants underwent an 8-day F, during which their sole intake was medium-mineralized water, consumed as desired (*ad libitum*). Prior to the study, medical screenings were conducted to ensure volunteers did not have chronic illnesses or dependencies on psychostimulant substances. All individuals received comprehensive information regarding the research methodology and potential risks. The study protocol received approval from the Research Ethics Committee.

Experimental protocol

Initial baseline data collected for each volunteer included age, body weight, height, and body mass index. Peripheral blood was drawn using a vacuum collection system and subsequently centrifuged at $1500 \times g$ for 15 minutes. Hematocrit (Ht) levels were measured immediately from the fresh blood samples. The resulting serum was separated and stored at -80 °C until further analysis.

Following initial blood collection, participants performed a physical exercise test, specifically a cycloergometric test engaging the lower limbs. The test commenced at a workload of 30 W, with subsequent increments of 30 W applied every 3 minutes. This progressive loading continued until participants reached their maximal exercise capacity, indicated by their inability to sustain the current workload. Blood samples were drawn again, following the previously described procedure, at 3 minutes and 1 hour post-exercise. This entire sequence, including baseline measurements, blood sampling, and the exercise test, was replicated after the 8-day fasting period.

Upon completion of both testing phases (pre- and post-fasting), the stored serum samples were analyzed for cytokines.

To assess exercise intensity, heart rate was measured at maximal load.

Furthermore, to verify adherence to the fasting regimen and assess the degree of physiological stress, serum concentrations of β -hydroxybutyrate (β -HB) and cortisol (C) were determined after the fasting period. These concentrations were quantified using Cortisol-CLIA assays (SNIBE Co., Ltd., Shenzhen, China) and the RANBUD kit (Randox Laboratories Ltd., Crumling, UK), respectively.

Assay methods

Bio-Plex Pro Human Inflammation Assays (Bio-Rad, USA) was used to analyze serum levels of pro- and anti-inflammatory cytokines. Concentrations of 27 mediators were assessed: interleukin-1 beta (IL-1 β), IL-1Ra, interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), IL-6, interleukin-7 (IL-7), IL-8, interleukin-9 (IL-9), IL-10, interleukin-12 p70 subunit (IL-12p70), interleukin-13 (IL-13), interleukin-15 (IL-

15), interleukin-17A (IL-17A), eosinophil chemotactic protein (Eotaxin), fibroblast growth factor basic (FGF basic), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma (IFN- γ), interferon gamma-induced protein 10/CXCL10 (IP-10), monocyte chemoattractant protein-1/CCL2 (MCP-1), macrophage inflammatory protein-1 alpha/CCL3 (MIP-1 α), MIP-1 β , platelet-derived growth factor BB (PDGF-bb), regulated upon activation, normal T cell expressed and presumably secreted/CCL5 (RANTES), TNF- α , and vascular endothelial growth factor (VEGF).

Statistical analysis

All collected data were expressed as mean \pm standard deviation (SD). For body weight and body mass index data, statistical comparisons were made using the Mann-Whitney U test. All other statistical analyses involved Friedman's rank analysis of variance for repeated measures, followed by the Dunn-Bonferroni post hoc test. These analyses were conducted using Statistica software, version 13.3 (TIBCO Software Inc.). A p-value of less than 0.05 was adopted as the threshold for statistical significance.

3. Results

The post hoc analysis revealed that F led to a significant reduction in somatic parameters and an increase in β -HB and C levels, whereas PhE resulted in a higher Ht value.

IL-8

IL-8 concentration increased statistically significantly after 8 days of fasting and immediately after the end of PhE (Table 1).

MIP-1 β

MIP-1 β concentration increased statistically significantly after 8 days of fasting and also 1 hour after the end of PhE (Table 1).

Other cytokines

For other cytokines, such as IL-1 β , IL-2, IL-6, IL-12p70, IFN- γ , TNF- α , IL-1Ra, IL-4, IL-5, IL-10, IL-13, IL-7, IL-9, IL-15, IL-17A, Eotaxin, FGF basic, G-CSF, GM-CSF, IP-10, MCP-1, MIP-1 α , PDGF-bb, RANTES, VEGF, no statistically significant differences in concentrations were demonstrated (Table 1).

Table 1. Concentration of selected cytokines in serum (Mean \pm SD).

Cytokine (pg/ml)	Before F	Before F, at once after PhE	Before F, 1 hour after PhE	After F	After F, at once after PhE	After F, 1 hour after PhE
IL-1 β	1.51 \pm 0.10	1.99 \pm 1.57	1.51 \pm 0.06	2.62 \pm 1.61	3.70 \pm 3.18	2.59 \pm 2.22
IL-1Ra	36.71 \pm 12.42	36.41 \pm 8.29	33.49 \pm 1.90	49.06 \pm 20.55	54.17 \pm 24.85	54.76 \pm 34.45
IL-2	0.35 \pm 0.05	0.35 \pm 0.03	0.34 \pm 0.04	0.36 \pm 0.05	0.33 \pm 0.02	0.34 \pm 0.04
IL-4	0.54 \pm 0.22	0.60 \pm 0.32	0.61 \pm 0.17	0.95 \pm 0.59	1.20 \pm 0.72	1.08 \pm 0.50

Cytokine (pg/ml)	Before F	Before F, at once after PhE	Before F, 1 hour after PhE	After F	After F, at once after PhE	After F, 1 hour after PhE
IL-5	1.87 ± 0.15	1.82 ± 0.18	1.92 ± 0.19	1.97 ± 0.17	1.92 ± 0.18	1.95 ± 0.19
IL-6	0.06 ± 0.06	0.03 ± 0.00	0.03 ± 0.00	0.04 ± 0.02	0.03 ± 0.00	0.03 ± 0.00
IL-7	15.54 ± 5.29	15.77 ± 5.17	15.77 ± 5.17	23.23 ± 12.61	28.54 ± 17.07	22.02 ± 17.46
IL-8	1.29 ± 0.82	1.42 ± 0.61	1.63 ± 0.73	3.42 ± 3.53	4.65 ± 2.87#	4.49 ± 3.05
IL-9	169.18 ± 55.49	169.13 ± 24.63	180.28 ± 32.71	163.89 ± 27.99	196.19 ± 33.04	208.50 ± 48.17
IL-10	1.04 ± 1.91	0.92 ± 1.61	1.00 ± 1.93	0.26 ± 0.02	0.25 ± 0.01	0.35 ± 0.14
IL-12p70	1.26 ± 0.81	0.90 ± 0.06	0.99 ± 0.05	0.98 ± 0.05	1.04 ± 0.08	1.01 ± 0.05
IL-13	0.12 ± 0.02	0.34 ± 0.52	0.13 ± 0.01	0.13 ± 0.01	0.14 ± 0.01	0.14 ± 0.01
IL-15	26.66 ± 1.39	24.55 ± 2.07	27.09 ± 2.07	27.42 ± 3.31	28.57 ± 3.20	27.30 ± 1.27
IL-17A	0.76 ± 0.37	0.65 ± 0.27	0.82 ± 0.37	0.81 ± 0.62	1.03 ± 0.41	0.98 ± 0.76
Eotaxin	9.73 ± 6.97	8.39 ± 6.43	8.86 ± 7.36	10.70 ± 10.77	14.12 ± 15.88	11.88 ± 11.75
FGF basic	15.02 ± 8.39	15.80 ± 6.36	12.77 ± 3.59	21.72 ± 6.91	24.39 ± 7.92	21.74 ± 5.08
G-CSF	6.08 ± 2.15	5.93 ± 3.49	5.39 ± 3.12	9.34 ± 6.93	11.45 ± 9.77	10.13 ± 4.50
GM-CSF	0.20 ± 0.03	0.20 ± 0.02	0.21 ± 0.01	0.21 ± 0.02	0.22 ± 0.02	0.18 ± 0.01
IFN-γ	0.44 ± 0.44	0.51 ± 0.17	0.33 ± 0.24	0.52 ± 0.26	0.64 ± 0.46	0.74 ± 0.37
IP-10	51.31 ± 27.94	58.06 ± 25.29	44.09 ± 16.49	37.14 ± 22.80	44.44 ± 27.89	43.21 ± 28.10
MCP-1	2.38 ± 1.48	3.37 ± 3.46	3.09 ± 2.80	3.70 ± 4.46	4.63 ± 6.42	3.90 ± 5.55
MIP-1α	1.00 ± 0.42	0.97 ± 0.48	0.92 ± 0.46	1.39 ± 0.94	1.69 ± 1.35	1.45 ± 0.77
MIP-1β	43.33 ± 9.58	45.57 ± 4.42	46.18 ± 7.14	47.85 ± 14.88	56.14 ± 12.72	56.77 ± 7.18#
PDGF-bb	345.07 ± 160.81	434.83 ± 230.16	362.75 ± 189.99	364.20 ± 221.45	395.80 ± 321.87	380.29 ± 265.86
RANTES	1441.97 ± 756.15	1511.18 ± 689.31	1907.50 ± 918.08	1749.65 ± 1171.92	1945.14 ± 550.47	2118.21 ± 1249.76
TNF-α	8.19 ± 4.83	7.49 ± 5.80	6.81 ± 3.52	8.24 ± 4.09	6.09 ± 2.50	8.69 ± 1.87
VEGF	1.93 ± 0.51	2.02 ± 0.26	1.87 ± 0.14	1.81 ± 0.27	2.24 ± 0.42	2.00 ± 0.25

p<0.05 vs. before F.

4. Discussion

The effect of F and PhE on IL-8 concentration

Serum IL-8 concentration increased statistically significantly after 8 days of F and immediately after completing PhE. IL-8 is a pro-inflammatory cytokin that plays an important role in recruiting neutrophils to inflammation sites [23]. Its increase after

F may indicate the induction of inflammation in response to a long-term lack of nutrient supply [24,25]. The increase in concentration after PhE is confirmed by many studies that have shown that intensive exercise leads to the activation of the immune system and an increase in the level of cytokines, including IL-8 [26-32,7]. Studies have shown that its concentration increases significantly during and immediately after PhE, playing a role in attracting neutrophils and initiating tissue regeneration [30]. Moreover, its participation in angiogenesis in skeletal muscles also suggests an adaptive function, promoting improved blood supply to working muscles [33].

The IL-8 response to 8 days of F may be of a different nature – on the one hand, it may be the result of oxidative stress caused by the lack of energy substrates and increased β -oxidation, and on the other hand, it may indicate the activation of the immune system as a result of intestinal dysbiosis and microbial translocation [34]. It is worth noting that IL-8 has been identified as a marker of endothelial activation and damage to epithelial barriers, which may additionally explain its increase in conditions of energy deficit.

The effect of F and PhE on MIP-1 β concentration

In the case of MIP-1 β (CCL4), a significant increase in concentration was observed only after 8 days of F and one hour after the end of PhE. MIP-1 β is involved in the recruitment of monocytes and NK cells to sites of inflammation [35-37]. Its delayed response after exercise suggests that the activation of this cytokin may result from the secondary phase of the immune response, and not from an immediate physiological reaction [38,31,7]. Similar observations were made by Cannon et al. [39], where MIP-1 β increased in response to muscle microinjuries in the regenerative phase. It can also be hypothesized that the increase in the concentration of this cytokin after F may suggest chronic activation of macrophages in response to energy deficiency and changes in fat metabolism. F activates the PPAR- α pathway and may cause the accumulation of lipid peroxidation products that induce the expression of MIP-1 β as part of the defense response [18].

No significant changes in other cytokines

No significant statistical changes were observed for the remaining 25 cytokines, including IL-1 β , IL-6, IL-10, TNF- α , and IFN- γ . The literature describes that the cytokine response to exercise and F is strongly dependent on the type, intensity, and duration of the stimulus [40-42,7]. The lack of changes may indicate a moderate level of inflammatory response in the study group, as well as a potential effect of the age of participants on the immune response [43,44].

Comparison with previous studies

Our results are consistent with the results of studies described by other authors. IL-8 increased after PhE in professional athletes [28] and in older people [29]. In turn, studies on F have shown that energy restriction can lead to a transient increase in inflammatory markers, including IL-8 and MIP-1 β [24,25]. Another experiment is the study conducted on semi-professional boxers, which showed that specific training regimens can modulate serum concentrations of cytokines such as IL-10, IL-15 and TNF- α after anaerobic exercise. This study suggested that boxing training may lead to attenuated pro-inflammatory response and induction of anti-inflammatory cytokines, which emphasizes the role of the type of training [45]. The impact of high metabolic stress, a factor also relevant in our study, is further underscored by research

in combat sports. For example, a study conducted on national-level judokas competing in consecutive bouts found significant metabolic stress, as indicated by high lactate levels, along with changes in physical performance parameters [46]. However, some studies indicate an anti-inflammatory effect of long-term F [47,18], which may depend on the length of the F and individual characteristics. At the same time, it should be remembered that factors such as metabolic stress, age, training, or hormonal conditions have a significant impact on the cytokine profile [47,36,37,48,31,38].

Potential Clinical Implications

The observed increase in IL-8 and MIP-1 β levels after an 8-day F period may be of significant importance for individuals undergoing therapeutic F or intensive one-time PhE. This may indicate the need to monitor inflammatory markers in these populations to prevent potential complications. Additionally, these results may be important in the context of therapies based on immune modulation, as well as in studies on aging and chronic low-grade inflammation [43,37,46,18].

Study limitations and future directions

It should be noted that the study was conducted on a limited number of participants. In the future, it would be advisable to conduct similar studies taking into account different F lengths, the level of physical fitness of participants and the type and intensity of exercise [49]. It would also be interesting to analyze the relationship between cytokine levels and intestinal microbiota .

5. Conclusions

8-day F leads to a statistically significant increase in serum levels of both IL-8 and MIP-1 β , suggesting activation of the body's inflammatory response under conditions of long-term energy deficiency. PhE causes a rapid increase in IL-8, observed immediately after the end of activity, indicating its role in neutrophil recruitment and muscle regeneration processes. MIP-1 β concentration increases only 1 hour after the end of PhE, suggesting its participation in the later phase of the immune response, associated with the activation of monocytes and T lymphocytes. The described differences in the time and mechanism of IL-8 and MIP-1 β activation indicate complementary roles of these cytokines in the body's response to physiological and metabolic stress. Both F and PhE can modulate the immune system, which may be important in planning dietary and training interventions, especially in people with chronic diseases or immune disorders, as well as in competitive sports.

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Ethics Approval: Approval was granted by the Research Ethics Committee of Jan Dlugosz University (JDU) in Czestochowa, Poland (Reference No. KE-U/9/2024).

Informed Consent Statement: This study used international research ethics guidelines, including the Declaration of Helsinki. All participating have given their informed consent.

Conflicts of Interest: The authors declare no conflicts of interest.

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