Illuminating insights: Exploring the effect of 16/8 intermittent fasting on serum cytokine levels in overweight adults

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Abstract

Background. The immune system's pivotal role extends to numerous diseases, and maintaining a balance between dietary and consumed energy is vital for preventing chronic illnesses and increasing life expectancy. Intermittent fasting (IF), a dietary approach typically implemented through time restrictions, exerts positive effects on the immune system and shows promising outcomes in managing various diseases.

Objectives. To evaluate the effectiveness of IF on the immune system with a wide cytokine panel.

Materials and methods. A total of 21 volunteers with body mass index (BMI) between 25 and 30 were included in the study. Fasting was applied for 16 h in a day to the volunteers, and they were free to consume food for the rest of the day. The weight, BMI, interleukin (IL)-1β, interferon (IFN)-α2, IFN-γ, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-23, and IL-33 values were measured using flow cytometry and compared before and after 21 days follow-up.

Results. The mean age of study participants was 37.76 ±8.06 years and weight loss of the volunteers was 3.35 percentile compared to the values obtained before fasting. The pro-inflammatory cytokines decreased, while anti-inflammatory cytokines increased after fasting; there was a significant difference in TNF-α, MCP-1, IL-6, IL-8, and IL-33 values. Also, IL-1β, IL-8 and IL-12p70 had moderately positive, IL-33 had strongly negative, and IL-10 had moderately negative correlation with the BMI change over time.

Conclusions. Intermittent fasting has positive effects on obesity-induced inflammation and promotes decrease in proinflammatory cytokines and increase in IL-33 values, which is known to have a protective effect on fat-associated inflammation.

Key words: obesity, inflammation, cytokine, IL-33, intermittent fasting

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Background

It is believed that maintaining a balance between dietary energy intake and energy expenditure plays a crucial role in preventing chronic diseases and increasing life expectancy.[1] Indeed, reports indicate that a long-term positive energy balance can lead to metabolic disorders caused by excessive weight gain and diseases such as type 2 diabetes mellitus, cardiovascular disorders, and low-grade inflammation-related diseases.[2] Additionally, it is hypothesized that lifelong reduction in food consumption (calorie restriction) significantly affects aging and lifespan in animals.[3]

Intermittent fasting (IF) regimens involve limited feeding periods and have historical roots in religious and spiritual traditions. Today, IF is regarded as a dietary intervention for weight loss and metabolic control.[1] Over recent years, numerous physiological effects of IF have been documented in studies involving rodents, monkeys and humans.[4] Notably, these effects include increased life expectancy, decreased mortality rates from cancers and cardiovascular diseases, improved insulin sensitivity, and reduced oxidative stress and inflammation.[5–8] Moreover, IF has been shown to significantly suppress inflammatory biomarkers such as interleukin (IL)-6 and C-reactive protein (CRP).[9,10]

Intermittent fasting and energy-restricting diets (ERDs) have the potential to partially slow down the aging process by mitigating systemic inflammatory status.[11] They achieve this primarily through diminishing the production of reactive oxygen species (ROS) and inhibiting gene expression linked to inflammatory responses at the tissue level.[12,13] Diets that simulate fasting i.e., fasting-mimicking diets (FMDs) have demonstrated beneficial effects in inflammatory diseases, such as rheumatoid arthritis, by regulating gastrointestinal microbiota, metabolism, and mitochondrial modulation throughout the day.[14]

Objectives

There are studies indicating that IF could reduce inflammation. However, these studies typically use only a few proinflammatory cytokines as markers. The aim of our study was to investigate the effects of IF on the immune system through a large group of cytokines that play a role in inflammation in order to explain the benefits of IF in many diseases.

Materials and methods

Patients

Following the approval of the Istanbul Training and Research Hospital Clinical Research Ethics Committee (approval No. 2534) for this observational cohort study, a public trial system application was submitted, and informed content was obtained from all volunteers (who were working in a hospital as healthcare workers). Participants volunteered to fast for 16 h a day and have an 8-h eating window between April 15, 2021, and May 5, 2021 (for a period of 21 days). Individuals with a body mass index (BMI) between 25 and 30 were included in the study during the month of Ramadan. According to the study protocol, volunteers fasted for 16 h between 04:00 AM and 08:00 PM and were permitted oral intake between 08:00 PM and 04:00 AM.

None of the volunteers participating in the study were subjected to any special diet program or calorie restrictions, and they were allowed to consume as much food as they wanted without any restrictions. The exclusion criteria were having known diabetes, cancer, immunodeficiency, or chronic inflammatory disease. The female volunteers were included in the study just after the end of their menstruation period, which resulted in the study lasting 21 days. Twenty volunteers were required for the study based on the power analysis, with a type 1 error as low as 0.05, a power as high as 0.95 and an effect size of 1.13, which was calculated from the expected BMI change.

Data collection and cytokine measurement

Volunteers were asked to note their food intake for the 3 days before starting the study and during the last 3 days of the study. Subsequently, the calorie intake and the amount and percent of carbohydrate, fat and protein they consumed before and during the IF period were calculated using the BeBis 8 computer program (EBISpro for Windows; EBISpro, Stuttgart, Germany). Their weight and height were measured, and blood samples were collected before and on the 21st day of the study. Blood samples were centrifuged at 1,800 rpm for 5 min to separate the serum. The levels of IL-1β, interferon (IFN)-α2, IFN-γ, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein-1 (MCP-1), IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-23, and IL-33 were measured in pg/mL using a Cube 8™ flow cytometer (Sysmex, Kobe, Japan; cat. No. CY-S-3068R_V3) and a LEGENDplex™ Human Inflammation Panel 1 cytokine measurement kit (BioLegend, San Diego, USA; cat. No. 740808) to assess the inflammation status as primary outcomes. The weight, BMI, consumed food components, and cytokine values were compared before and after the 21 days of IF.

Patient follow-up

Daily face-to-face communication was established with the volunteers to assess whether they continued to meet the study conditions. At the beginning of the study, 27 volunteers were included. However, during the study, 1 volunteer contracted coronavirus disease-19 (COVID-19), and 5 did not fulfill the fasting criteria for 1 or more days, resulting in 6 volunteers being excluded from the study.

Statistical analyses

Data analysis employed IBM SPSS v. 26.0 (IBM Corp., Armonk, USA), with the Shapiro–Wilk test assessing the normality of the distribution of the differences. If the differences were normally distributed, they were expressed as mean ±standard deviation (M ±SD), otherwise as median and interquartile range (IQR). In the analysis, paired t-tests compared dependent and normally distributed differences, and Wilcoxon's signed-rank test evaluated dependent and non-normally distributed differences. Pearson's correlation coefficients examined BMI change. The interpretations of the correlation analysis were very weak (0.00–0.19), weak (0.20–00.39), moderate (0.40–0.59), strong (0.60–0.79), or very strong (0.80–1.0). The statistical significance level of the data was accepted as $p < 0.005$.

Results

The mean age of the volunteers was 37.76 ±8.06 years, and the mean BMI was 27.93 ±1.12. The study comprised 9 women and 12 men. After 21 days, the volunteers had lost 3.35 ±1.29% of their weight, which was significant compared to pre-IF levels ($p < 0.001$). Additionally, there were significant reductions in energy intake and the amounts of carbohydrate, protein, and fat intake at the end of the study ($p < 0.001$ for all) (Table 1).

It was determined that the TNF-α, MCP-1, IL-6, and IL-8 values were significantly lower after the IF period, while IL-33 concentration was significantly higher compared to the pre-IF values ($p = 0.022$, $p = 0.030$, $p = 0.025$, $p = 0.004$, $p = 0.0017$, and $p = 0.011$, respectively). Furthermore, IL-10 levels were slightly higher, and IFN-α2, IL-12p70, and IL-18 measurements were slightly lower.

Table 1. Evaluation of daily energy and macronutrient intake and weight-BMI status before and after 21 days of follow-up

Parameters	Before fasting	After fasting	p-value	95% CI of the difference (lower)–(upper)	t or Z value
Weight (kg) (M ±SD)	83.81 ±10.71	81.00 ±10.42	<0.001[a]	(2.31)–(3.30)	11.94[#]
BMI (M ±SD)	27.93 ±1.12	26.98 ±0.87	<0.001[a]	(0.76)–(1.12)	11.01[#]
Energy intake (kcal) (M ±SD)	2443.18 ±352.55	1846.69 ±359.12	<0.001[a]	(473.61)–(719.37)	10.12[#]
Carbohydrate intake (g) (M ±SD)	300.64 ±66.39	226.79 ±65.42	<0.001[a]	(54.09)–(93.61)	7.79[#]
Carbohydrate intake (%) (M ±SD)	50.14 ±7.65	49.38 ±7.57	0.576[a]	(–2.03)–(3.55)	0.56[#]
Protein intake (g) (median – IQR)	82.40–33.60	66.20–20.45	<0.001[b]	(0.00)–(0.13)	–4.01*
Protein intake (%) (M ±SD)	13.57 ±2.69	14.67 ±1.90	0.083[a]	(–2.34)–(0.15)	–1.82[#]
Fat intake (g) (M ±SD)	98.16 ±21.14	73.09 ±14.09	<0.001[a]	(16.34)–(33.79)	5.99[#]
Fat intake (%) (M ±SD)	35.96 ±7.23	35.85 ±6.55	0.932[a]	(–2.19)–(2.38)	0.08[#]

[a] paired sample t test; [b] Wilcoxon signed-rank test; [#] t value; * Z value; 95% CI – 95% confidence interval; M ±SD – mean ±standard deviation; BMI – body mass index; IQR – interquatile range; df is 20 for all the variables.

Table 2. Comparison of blood cytokine values before and after 21 days of follow-up

Parameters	Before fasting	After fasting	p-value	95% CI of the difference (lower)–(upper)	t or Z value
IL-1β pg/mL (M ±SD)	58.87 ±36.03	53.94 ±48.05	0.470[a]	(–9.02)–(18.88)	0.73[#]
IFN-α2 pg/mL (median – IQR)	1.82–3.14	1.59–1.47	0.205[b]	(0.02)–(0.35)	–1.26*
IFN-γ pg/mL (median – IQR)	1.11–9.51	1.20–2.91	0.244[b]	(0.02)–(0.35)	–1.16*
TNF-α pg/mL (median – IQR)	29.00–38.44	0.02–18.17	0.022[b]	(0.00)–(0.13)	–2.29*
MCP-1 pg/mL (median – IQR)	312.50–354.26	286.56–198.12	0.030[b]	(0.00)–(0.13)	–2.17*
IL-6 pg/mL (M ±SD)	5.89 ±5.06	4.66 ±3.74	0.028[a]	(0.15)–(2.31)	2.37[#]
IL-8 pg/mL (M ±SD)	39.03 ±28.23	21.46 ±22.30	0.003[a]	(6.52)–(28.62)	3.16[#]
IL-10 pg/mL (median – IQR)	3.91–4.57	4.27–6.30	0.108[b]	(0.00)–(0.22)	–1.60*
IL-12p70 pg/mL (median – IQR)	2.39–4.50	2.08–1.27	0.289[b]	(0.02)–(0.35)	–1.06*
IL-17A pg/mL (median – IQR)	0.11–0.45	0.10–0.36	0.390[b]	(0.17)–(0.58)	–0.85*
IL-18 pg/mL (median – IQR)	172.74–117.38	161.87–148.48	0.394[b]	(0.31)–(0.73)	–0.85*
IL-23 pg/mL (median – IQR)	10.03–26.92	8.20–19.27	0.065[b]	(0.00)–(0.13)	–1.84*
IL-33 pg/mL (median – IQR)	31.32–119.53	81.34–276.07	0.011[b]	(0.00)–(0.13)	–2.55*

[a] paired sample t test; [b] Wilcoxon signed-rank test; [#] t value; * Z value; 95% CI – 95% confidence interval; M ±SD – mean ±standard deviation; IL – interleukin; IFN – interferon; TNF – tumor necrosis factor; MCP – monocyte chemoattractant protein; IQR – interquatile range; df is 20 for all the variables.

Table 3. The correlation results of % change of the parameters according to % BMI change after 21 days of intermittent fasting

Parameters	Correlation (p, r)	
	p-value	r-value
Weight	1.000	0.000
IL-1β	0.009	0.553
IFN-α2	0.078	0.393
IFN-γ	0.115	0.354
TNF-α	0.145	0.329
MCP-1	0.055	0.424
IL-6	0.624	–0.114
IL-8	0.018	0.510
IL-10	0.024	–0.490
IL-12p70	0.046	0.440
IL-17A	0.115	0.354
IL-18	0.113	0.357
IL-23	0.160	0.318
IL-33	<0.001	–0.729
Energy intake	<0.001	0.749
Carbohydrate (g)	0.012	0.539
Carbohydrate (%)	0.837	0.048
Protein (g)	0.095	0.374
Protein (%)	0.200	–0.291
Fat (g)	0.004	0.601
Fat (%)	0.483	0.162

BMI – body mass index; IL – interleukin; IFN – interferon; TNF – tumor necrosis factor; MCP – monocyte chemoattractant protein.

However, these differences were not statistically significant (Table 2).

The correlation analysis of BMI changes revealed that IL-1β, IL-8, IL-12p70, and the amount of carbohydrate intake had a moderate positive correlation, while energy intake and the amount of fat intake exhibited a strong positive correlation, IL-33 showed a strong negative correlation, and IL-10 demonstrated a moderate negative correlation (Table 3).

Discussion

Excessive caloric intake and subsequent development of obesity are characterized by a chronic state of inflammation involving increased levels of circulating proinflammatory cytokines, described as "low-grade inflammation."[15] In this situation, a 2-to-3-fold increase in systemic concentrations of TNF-α, IL-1β and IL-6 is typically observed,[16] which may contribute to the induction of autoimmune diseases such as rheumatoid arthritis and inflammatory conditions, including atherosclerosis, insulin resistance, cardiovascular diseases, and tissue damage associated with many types of cancer.[17]

There are numerous publications examining the effects of IF on serum cytokines, with most reporting a decrease in proinflammatory cytokines. Furthermore, IL-1β, IL-6, and TNF-α have been shown to significantly decrease after Ramadan fasting (RF), which serves as an IF model.[17] Additionally, significant decreases in body weight, BMI, IL-2, IL-8, and TNF-α have been reported in obese men after RF, not just in men with a normal BMI.[18] Another study states that RF can significantly reduce all anthropometric parameters, IL-6, and CRP in patients with nonalcoholic fatty liver disease.[19] In our study, we observed a significant regression of proinflammatory TNF-α, IL-6, and IL-8 after IF, although IL-1β decreased by an insignificant amount. Moreover, we found a moderate positive correlation between the decrease in BMI and IL-1β and IL-8 values.

There are studies reporting an increase in IL-10 after IF, which plays an anti-inflammatory role. One such study reported that, while proinflammatory cytokines decreased during a 4-week RF, the IL-10 value increased significantly.[20] Another study found a significant increase in IL-10 levels after RF.[21] In our study, we observed an increase in IL-10 levels after IF, although it was not statistically significant. Additionally, this increase showed a moderate negative correlation with BMI.

The MCP-1 is a crucial chemokine that plays a significant role in many diseases. It binds to C-C chemokine receptor type 2 (CCR2), activating signaling pathways that regulate leukocyte migration. Studies have reported higher MCP-1 levels in patients with obesity than in lean individuals.[22,23] However, there are few studies in the literature evaluating the effect of IF on MCP-1. In an animal study, mice were subjected to a high-fat diet for 3 days, followed by 1 day of fasting for 7 or 14 weeks. They were compared with rats that received a continuous high-fat diet, and it was observed that MCP-1 levels decreased significantly in both the 7- and 14-week IF groups compared to the continuous high-fat diet group.[24] In obese mice, calorie restriction has been shown to significantly reduce messenger ribonucleic acid (mRNA) expression levels of several inflammatory cytokines and chemokines in white adipose tissue, including MCP-1.[25] In our study, we observed a significant decrease in MCP-1 levels after IF-induced weight loss.

Interleukin 17A, released from T-helper 17 (Th17 cells), and IL-23, an important cytokine for Th17 development, are related to autoimmunity. Evidence suggests that the Th17 cell number increases while regulatory cells decrease in obesity.[26] However, there are very few studies evaluating IL-17 and IL-23 values in obesity and the effect of IF on these cytokines. Some studies have reported higher IL-17 and IL-23 levels in obese individuals,[27] and it has been observed that IL-23 values significantly decrease after an intermittent ERD.[28] We found that the IL-17A and the IL-23 values decreased after IF; however, these differences did not reach statistical significance. This lack of significance could be attributed to the relatively short duration of the IF period or only including overweight individuals.

Interleukin 33 is a cytokine belonging to the IL-1 family that induces type 1 and type 2 immune responses by binding to the tumorigenicity 2 (ST2) receptor. The literature reports that IL-33 has a protective effect on adipose tissue, shielding it from inflammation.[29] In a study by Hasan et al., who investigated the relationship between serum IL-33 levels and BMI of lean and obese individuals, overweight study participants had lower serum IL-33 levels than lean individuals, and a negative correlation was observed between IL-33 and BMI.[30] There is only 1 study investigating the effect of intermittent ERD on IL-33 values, which reported that IL-33 values were significantly lower in intermittent ERD patients. However, our study found that IL-33 values increased significantly after IF, and there was a strong negative correlation with the change in BMI, suggesting that the increase in IL-33 may be linked to its inflammation-reducing effect on adipose tissue.

In the literature, there are only a few studies evaluating the effects of IF on IL-12p70, IL-18, IFN-γ, and IFN-α2 serum levels. In a study of 28 obese patients divided into 2 groups, 1 group was administered on a 3 nonconsecutive day intermittent ERD for 12 weeks, during which the patients consumed 550 kcal/day for women and 650 kcal/day for men. The other group received a continuous ERD with a low-calorie diet (LCD) of 33% energy restriction. Among the groups, IFN-γ, IL-18 and IL-23 values were significantly lower in patients on an intermittent ERD.[28] Our study found that IL-12p70, IL-18, IFN-γ, and IFN-α2 decreased after IF; however, these differences did not reach statistical significance.

Limitations

Study limitations include the limited number of volunteers, not comparing the volunteers with different BMI categories, using kit-dependent cytokine measurements within specific intervals, and only evaluating a 3-week period. Additionally, no special diet program or calorie restriction was applied to any volunteers participating in the study. While this situation might suggest that the results could be influenced by variations in food intake among individuals, efforts were made to address this concern by setting up each volunteer with their own control.

Conclusions

The immune system plays the most important role in many diseases. There are publications discussing the benefits of IF on cancer and various diseases, but the impact of IF on the immune system remains unclear in explaining the benefits of IF on these conditions. Our study is one of the rare investigations evaluating the effects of IF on the immune system. According to our results, IF led to a significant decrease in proinflammatory cytokines and a significant increase in IL-33 levels, which is known to have protective effects against inflammation in adipose tissue. These findings support that IF is an effective dietary approach that promotes weight loss and could potentially reduce obesity-related inflammation by decreasing BMI; long-term studies are needed on this subject.

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