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ORIGINAL PAPER

The effect of intermittent fasting 5:2 on IL-6 levels in obese male employees in Jakarta

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Abstract

Background: Obesity is a condition of excessive fat accumulation in adipose tissue. This condition causes endothelial damage, increase macrophage infiltration, and inflammation in adipose tissue. Inflammation happens due to the increase of interleukin-6 (IL-6) as a proinflammatory cytokine which responsible for the occurrence of chronic diseases. Intermittent fasting is a potentially effective method for losing weight and suggested can reduce levels of proinflammatory cytokines.
Objective: The aim of this study is to determine the effect of 5:2 intermittent fasting on IL-6 cytokine levels in obese employees in Jakarta.
Methods: This study used a cross-sectional method conducted on 50 healthy male employees aged 19–52 years with a body mass index (BMI) ≥25 kg/m2. Subjects were divided into two groups, the 5:2 intermittent fasting group and the non-fasting group. Intermittent fasting 5:2 was observed every Monday and Thursday for eight weeks. IL-6 levels were obtained through examination using an enzyme-linked immunosorbent assay (ELISA) method. Statistical analysis was performed by Mann Whitney and Kruskal Wallis test.
Results: The results showed that the median of IL-6 levels decreased in fasting group from 5,10 (1.06–9.81) pg/mL to 4.64 (1.00–13.39) pg/mL and increased in non-fasting group from 3.65 (1.17–38.70) pg /mL to 6.35 (2.44–19.86) pg/mL, but the change was not significant.
Conclusion: Intermittent fasting 5:2 tend to decrease IL-6 levels in obese male employees in Jakarta although the change of IL-6 level was not significant.

Keywords: obesity, male employees, interleukine-6, intermittent fasting 5:2

Introduction

Based on data from the World Health Organization, 650 million people in the world are included in the obese group.[1] In Indonesia, obesity is a nutritional problem that continues to increase every year. The obesity rate in Indonesia tends to increase every year, from 10.5% in 2007 and 14.8% in 2013 to 21.8% in 2018.[2] Data from the 2013 Riskesdas found that obesity is more common in people with high economic levels, for example office workers.[3] A study showed that out of 174 office workers in Jakarta, 59% were in the less physically active category and 19% did not do any physical activity at all. As many as 63.3% of subjects in the less physically active category were obese.[4]

Enlargement of adipose tissue in obesity, causes blood supply to adipose tissue to be reduced. Endothelial damage in adipose tissue leads to macrophage infiltration and local inflammation in

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adipose tissue. Adipose tissue machrophage (ATM) secretes proinflammatory cytokines, and an increased levels of IL-6 can lead to dysregulation of fatty acid metabolism in adipose tissue. In addition, obesity-induced IL-6 secretion plays a role in systemic inflammation which contributes to various other disease processes such as insulin resistance, cardiovascular disease, and malignancy.[4–6] Therefore, IL-6 examination is important to see the predisposition to inflammation through increased IL-6 inflammatory mediators.

Intermittent fasting is one method that is considered effective for losing weight and changing the body's metabolism as well as proven can reduce the levels of inflammation indicators such as tumor necrosis factor – α (TNF- α) and IL-6. Intermittent fasting has several regimens, including complete alternate-day fasting, modified fasting regimens, time-restricted feeding and religious fasting. Intermittent fasting 5:2 is a type of modified fasting regiment by fasting for two non-consecutive days a week and five non-fasting days.[7–8] The decreased of IL-6 levels after intermittent fasting has been found in several studies. There is a study by Razavi, et al.[9] which compared IL-6 levels in people who did intermittent fasting and calorie restriction. As a result, intermittent fasting can lower IL-6 levels more than calorie restriction.

Our previous study analyzed the effect of 5:2 intermittent fasting for eight weeks on malondialdehyde (MDA) and catalase levels in obese male employees. MDA levels in the 5:2 intermittent fasting group significantly decreased from 1.3 nmol/mL to 0.4 nmol/mL compared to the non-fasting group.[10] Based on the findings above, we determined to examine whether 5:2 intermittent fasting could also decrease IL-6 level. Research on 5:2 intermittent fasting has not been widely carried out in Indonesia and in particular there has been no study assessing a 5:2 intermittent fasting effects on IL-6 in obese employees. Therefore, the objective of this study was to examine the effect of 5:2 intermittent fasting on IL-6 levels in obese male employees in Jakarta.

Methods

Subject Study

This research has received approval from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia with the certificate number of passing the ethical review KET-126/UN2.F1/ETIK/PPM.00.02/2023. Subjects were taken from secondary research data that had been previously conducted by Yudhistina, et al.[10] The data collection in this study was by taking subjects from medical records kept by the company. Initial screening was carried out in male employees with obesity and subjects who met the study criteria were given an information sheet about the research. After understanding the information provided, subjects who were willing to participate in the study were asked to sign a consent form. Involvement of subjects in research is voluntary and the data obtained is confidential.

This study was taken using the total sampling method from stored samples from previous study. The sample for this study came from 50 male employee aged 19–52 years with a body mass index (BMI) ≥25 kg/m^2. Subjects were divided into two groups, the 5:2 intermittent fasting group and the non-fasting group.

Methodology and Sampling Method

The research design used was cross sectional on stored samples from previous studies. Clinical trials have been carried out in a previous study which assessed the effect of 5:2 intermittent fasting on oxidative stress in obese employees.[10] Laboratory examinations were carried out on plasma samples stored in the laboratory of the Department of Biochemistry & Molecular Biology, Faculty of Medicine, Universitas Indonesia, Jakarta.

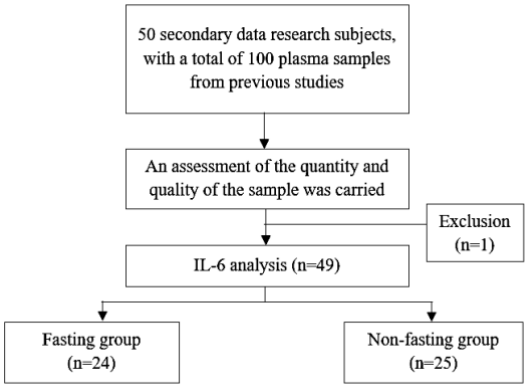

Figure 1. Research subject selection

Sample selection was carried out to determine which samples were in a state of non-lysis and sufficient to be included in this study (**Figure 1**). Secondary sample laboratory tests were conducted to determine IL-6 levels as a molecular marker of inflammation in the body using enzyme linked-immunosorbent assay (ELISA) method. One subject was excluded because the quantity of plasma samples was insufficient for examination.

Analysis of subject characteristics, food intake and nutritional status

Individual characteristics were determined through interviews that have been conducted in previous studies.[10] Age, general identity, education level, nutrition awareness level, type of work, and income level are some of the information collected in primary data. The previous study measured food intake both before and during intervention. The 2x24 hour food recall method was used to assess food intake prior to the study, with the aim of determining the eating pattern of the research subjects prior to intervention. In the 5th week of the intervention, 2x24 hour food recall was carried out to determine the subject's food intake during the intervention phase.[10]

The food record approach was used with the aim of determining how the study subject's food intake pattern was during the intervention. Food intake in the fasting group was obtained by asking participants to record the amount and type of food eaten at dawn and iftar, while food intake in the control group was determined by recording three food records (two weekdays and one weekend). Enumerators conducted interviews with photo books of food ingredients from the Ministry of Health of the Republic of Indonesia and food models which were carried out on weekdays and holidays. The data was then analyzed using the 2007 nutrisurvey program.

Analysis of IL-6 levels

Blood samples in the previous study were taken from the subject's cubital fossa after the area was sterilized with alcohol cotton. Specimens were taken as much as 3 ml of blood stored in a tube labelled with the identity of the subject. Plasma samples were stored in the -20˚C refrigerator. Sample selection was carried out to determine samples that were in a state of non-lysis to be included in this study. The IL-6 levels as a molecular marker of inflammation in the body was examined using the ELISA method (Elabscience, United State) followed manual instruction. The change of IL-6 level was presented as a ratio by dividing IL-6 level post intervention with pre intervention both in fasting and non-fasting group.

Statistical analysis

Data analysis was conducted using SPSS software version 20. The design of data analysis consisted of univariate analysis, the data on numerical scale variables were tested for normality with the Kolmogorov-Smirnov test. Data with a normal distribution are presented in the mean ± standard deviation and data with an abnormal distribution are presented in the median. Categorical scale variable data is presented in frequency. Bivariate analysis was performed to test the means of the two unpaired groups using the independent t-test if normally distributed and Mann Whitney if not normally distributed. Categorical data test using Kruskal Wallis. Correlation test was performed using the Spearman test.

Results

IL-6 Levels Based on the Characteristics of Research Subjects

Table 1. IL-6 Levels Based on the Characteristics of Research Subjects

Variable	IL-6 Levels (pg/mL)	p-value
Nutritional status, median (min-max)		0.154 [mw]
Obese I (n=20)	5.10 (1.06–18.40)	
Obese II (n-29)	3.90 (1.06–38.70)	
Physical activity, median (min-max)		0.460 [kw]
Mild (n=19)	6.00 (1.45–38.70)	
Moderate (n=23)	4.18 (1.06–11.00)	
Severe (n=7)	3.90 (1.06–7.31)	
Smoking history, median (min-max)		0.936 [kw]
Non-smoker (n=19)	5.00 (1.17–8.73)	
Low (n=17)	3.90 (1.06–11.00)	
Intermediate-high (n=13)	4.30 (1.06–38.70)	

[mw]: Mann-Whitney test, [kw]: Kruskal Wallis test

Table 2. IL-6 Levels in Fasting and Non-Fasting Group

IL-6	Group		p-value
	Fasting	Non-fasting	
Before, median (min-max) pg/mL	5.10 (1.06–9.81)	3.65 (1.17–38.70)	0.435 [m]
After, median (min-max) pg/mL	4.64 (1.00–13.39)	6.35 (2.44–19.86)	0.200 [m]
Ratio, median (min-maks)	0.79 (0.19–7.19)	1.82 (0.08–14.81)	0.407 [m]
p-value	0.853 [w]	0.930 [w]	

[m]: Mann-Whitney test, [w]: Wilcoxon

Characteristics of research subjects based on previous research, the age of research subjects has a median value of 32 (19-52) years in the fasting group and 30 (22-54) years in the control group. The mean height of the subjects in the fasting group was 168.3 ± 5 cm and 168.5 ± 6.5 cm in the non-fasting group. Subjects's body weight in the fasting group had an average of 90.5 kg and in the non-fasting group 89.6 kg. The average BMI of fasting subjects was 32.7 ± 4.1 kg/m2 and that of non-fasting subjects was 31.7 ± 4.3 kg/m^2. IL-6 levels based on the characteristics of the research subjects can be seen in **Table 1**.[10]

IL-6 Levels in Fasting and Non-Fasting Group

IL-6 levels in the fasting group decreased from 5.10 pg/mL to 4.64 pg/mL, while in the non-fasting group the IL-6 levels increased from 3.65 pg/mL to 6.35 pg/mL. However, these changes were not statistically significant.

The difference in IL-6 levels in the fasting and non-fasting groups before the intervention was not significant, with a p-value of 0.527. There was also no significant difference in IL-6 levels in the fasting and non-fasting groups after the intervention, with a p-value of 0.176. Because change in subject's IL-6 level was vary in the form of decrease and increase, therefore changes in IL-6 levels were presented as a ratio to facilitate data analysis. The p-value of the fasting and non-fasting groups in the ratio of changes in IL-6 levels was 0.407, the changes in IL-6 levels in the fasting and non-fasting groups were not significantly different, as shown in **Table 2**.

Changes in IL-6 Levels Based on Subject Characteristics

In our previous study, the weight subjects in the fasting group experienced a significant change ($p < 0.05$), namely 90.8 ± 13.5 kg before the intervention to 90.0 ± 13.4 kg after the intervention, with a change value of 0.8 (-2.2–5.1) kg ($p = 0.015$).[10] Changes in body weight in the non-fasting group experienced was not significant ($p>0.05$), namely 89.6 ± 12.8 kg before the intervention and 89.3 ± 12.6 kg after the intervention. However, no

significant difference was found in body weight between the fasting and non-fasting groups (p>0.05).[10] In order to know the effect of body weight change toward IL-6 level change, correlation analysis was performed. The correlation coefficient was 0.120 in fasting group and 0.028 in non-fasting group with a p value >0.05, indicating that there was no correlation between changes in body weight and the ratio of changes in IL-6 (**Table 3**).

Table 3. Correlation Analysis of Changes in Body Weight to the Ratio of Changes in IL-6

Variable	Correlation coefficient (r)	p-value
Fasting (n=24)		
Body weight	0.120	0.576 [s]
Non-fasting (n=25)		
Body weight	0.028	0.892 [s]

[s]: Spearman Correlation test

Changes in IL-6 levels were calculated as ratio values in the fasting and non-fasting groups and were analyzed based on the characteristics of the subjects (**Table 4**). Relationship between respondent characteristics and changes in IL-6 levels indicate a p-value for each respondent characteristic is greater than 0.05. It can be concluded that changes in IL-6 levels were not affected by the characteristics of the research respondents.

This study conducted a correlation analysis between changes in the ratio of IL-6 levels and data on changes in total energy, protein, carbohydrates and fat that obtained from previous studies.[10] In **Table 5**, it can be seen that in the fasting and non-fasting groups there was no correlation changes in total energy, protein, carbohydrates and fat to changes in the IL-6 ratio (p> 0.05)

Table 4. Factors Affecting IL-6 Levels

Variable	Ratio changes in IL-6 levels, median (min-max)		p-value	
	Fasting (n=24)	Non-fasting (n=25)	Fasting	Non-fasting
Nutritional status			0.929[mw]	0.913[mw]
Obese I	0.93 (0.19–5.72)	1.34 (0.27–8.58)		
Obese II	0.80 (0.32–14.81)	1.77 (0.16–5.05)		
Physical activity			0.870 [kw]	0.457 [mw]
Mild	1.73 (0.31–14.81)	1.72 (0.16–8.58)		
Moderate	0.89 (0.19–7.19)	1.26 (0.27–3.04)		
Severe	0.91 (0.32–5.72)	2.52 (1.82–3.24)		
Smoking history			0.079 [kw]	0.951 [kw]
Non-smoker	0.80 (0.19–2.67)	1.58 (0.45–8.58)		
Low	4.82 (0.63–14.81)	1.72 (0.27–5.05)		
Intermediate-high	3.11 (0.32–6.98)	1.40 (0.27–5.05)		

[kw]: Kruskal Wallis test, [mw]: Mann-Whitney test

Table 5. Correlation Analysis of Changes in Nutrient Intake to The Ratio of Changes in IL6

Variable	Correlation coefficient (r)	p-value
Fasting (n=24)		
Total energy change	0.080	0.710 [s]
Total carbohydrate change	0.077	0.722 [s]
Total protein change	0.138	0.519 [s]
Total fat change	0.223	0.296 [s]
Non-fasting (n=25)		
Total energy change	0.125	0.550 [s]
Total carbohydrate change	0.020	0.924 [s]
Total protein change	0.100	0.634 [s]
Total fat change	0.162	0.440 [s]

[s]: Spearman Correlation test

Discussion

Subjects in the obese II category had a lower median IL-6 level (3.90 pg/mL) compared to obese I (5.10 pg/mL) and the highest level of IL-6 was found in subjects in the obese category II with levels of 38.70 pg/mL however it was not significant. Normal IL-6 levels for healthy adults are 0.2– 7.8 pg/mL.[11] Several studies have shown that obese individuals have higher IL-6 levels.[12-14] In this study, the lowest IL-6 level was 1.06 pg/mL and the highest was 38.70 pg/mL detected in obese male subjects. Intermittent fasting 5:2 caused a decrease in IL-6 levels in the fasting group and an increase in IL-6 levels in the non-fasting group, however these changes were not significant both in the fasting group (p=0.602) and in the non-fasting group (p=0.621). This result similar with other study in 2020 which comparing calorie restriction and alternate day fasting. They did not detect any significant changes in TNF-α (p=0.60) and IL-6 (p=0.49) in both groups but found a significant reduction in High sensitivity C-Reactive Protein (hsCRP) levels (p=0.03).[9] Trepanowski JF, et al.[15] conducted a study with similar results by comparing calorie restriction, alternate day fasting and controls. The results found that the comparison of fat-free mass with total mass ratio decreased significantly in both groups, but IL-6 levels did not change significantly in the three groups (p=0.99).[15] Study using the fasting time-restricted feeding method for five weeks compared fasting and control groups showed that time-restricted feeding reduced oxidative stress but did not affect inflammation markers. The results show decreased plasma levels of 8-isoprostane, a marker of oxidative stress (p=0.05), however, it did not affect inflammation markers hsCRP (p=0.77) and IL-6 (p=0.12).[16]

Other study proved the different result by examining the effect of Ramadan intermittent fasting on inflammatory biomarkers in obese male subjects. Biomarker inflammation was measured four times, 24 hours before Ramadan, the 15th day of Ramadan, one day after Ramadan and 21 days after Ramadan. The results showed that there was no significant change in hsCRP (p=0.3), but significant in the levels of IL-6 (p=0.02) and TNF-α (p=0.01) in the fasting group compared to the control group.[17] Intermittent fasting can reduce fat mass in adipose tissue, therefore adipose tissue hypertrophy will decrease. Moreover, decreased macrophages will inhibit the production of IL-6, TNF-α and IL-1.[18]

The correlation analysis of weight changes to the ratio of IL-6 changes in this study yielded a correlation coefficient in the fasting group of 0.120 and a correlation coefficient in the non-fasting group of 0.028, indicating that there was no correlation between weight changes and the ratio of IL-6 changes. According to research evaluating the impact of Ramadan intermittent fasting on pro-inflammatory cytokine levels, body weight decreased significantly (p<0.001) from 71.82 ± 13.41 kg to 70.58 ± 13.20 kg and IL-6 levels decreased from 155.85 ± 121.18 pg/mL to 67.42 ± 51.25 pg/mL, however body weight did not significantly correlate with IL-6, IL-1ß, and TNF-α.[18] Other study shows a link between BMI and IL-6 levels was discovered in a different study (r=0.84, p<0.05).[12] Interleukin-6 is a pro-inflammatory cytokine secreted by adipose tissue and it expresses mRNA for IL-6, so weight loss can affect IL-6 levels.[14]

The characteristics of respondents with changes in IL-6 levels showed p value is greater than 0.05, so it can be concluded that changes in IL-6 levels are not affected by the characteristics of the research respondents in this study. Research conducted with 62 participants received one of three interventions; aerobic exercise, combined aerobic and resistance exercise, or control. After 12 weeks of intervention, there was a reduction in body fat and IL-6 in the aerobic group (p=0.01) and the combination of aerobics and resistance training (p=0.01) and no changes in the control group.[19] Adipose tissue fat can lessen during vigorous exercise, which in turn lessens the production of cytokines that promote inflammation.[20] In addition, high levels of IL-6 are also thought to be linked to smoking. Al-Tameemi SA, et al.[21] conducted a study with 108 smokers and 51 non-smokers. IL-6 (2.58 ± 0.98 pg/mL) and TNF-α (28.38 ± 7.162 pg/mL) levels in the smoking group were higher

than non-smokers (IL-6: 22.64 ± 7.257 pg /mL and TNF-α: 22.64±7.257 pg/mL).

Changes in total energy, carbohydrates, protein and fat in this study had no correlation with the ratio of IL-6 reduction (p>0.05) in the fasting and non-fasting groups. This result has a similar finding with a study examining the effect of 6-week Dietary Approaches to Stop Hypertension (DASH) on inflammatory biomarkers in children with an average age of 14 years with metabolic syndrome. The type of diet using DASH is designed to be rich in fruits, vegetables, whole grains and low-fat dairy products and low in saturated fat. The study found insignificant result in the levels of TNF-α, IL-6 and IL-2 (p> 0.05), however a significant change was detected in CRP levels (p=0.002) in the DASH group when compared to the group that received general dietary advice only.[22] Another study divided into two groups of very low-carbohydrate high-fat (VLCHF) subjects and their daily habitual diet. After four weeks of intervention, there was no significant difference in adiponectin and IL-6 levels in the two groups (p>0.05).[23] Nevertheless, other studies found that dietary intake influences IL-6. A research assessed the relationship of dietary inflammatory index to inflammatory markers showed a positive relationship between dietary inflammatory index and IL-6 (OR 1.19, 95% CI). The study concluded that increased levels of IL-6 can occur when consuming pro-inflammatory food components such as cholesterol and saturated fat, and relatively low levels of anti-inflammatory food components such as fruits and vegetables.[24] When a person consumes a high intake of fat, free fatty acids will be increased causing increased production of IL-1ß, TNF-α and IL-6. High fat intake also increases NF-κß in the liver which plays a role in increasing proinflammatory cytokines. This sustainable diet will lead to systemic inflammation. Other research also found that the group of people who consumed a healthy diet, namely those with a high intake of low-fat dairy products, fruit, whole grains, poultry, fish and vegetables, had lower IL-6 levels and fasting blood sugar than the group that consumed a high-fat diet (p<0.05).[25]

Our previous study conducted using the same subjects showed that intermittent fasting 5:2 significantly decreased malondialdehyde (MDA) as oxidative stress marker, it turns out that the decrease in MDA was not accompanied by a statistically significant decrease in IL-6 levels.[10] The evaluation of IL-6 levels may be affected by the limitations of this study. Several factors were probably affecting IL-6 level which was not analyzed in this study such as the subject's sleep quality factors. Elevated levels of IL-6 are found in individuals who experience sleep disturbances at night and are sleepy during the day, such as in conditions of excessive daytime sleepiness and obstructive sleep apnoea.[26] In addition, there was no calorie restriction intervention to the subjects during non-fasting period. According to research, fasting throughout Ramadan without restricting calories considerably reduced body weight from 90.8 (72.2-109.4) kg to 89.4 (70.9-107.9) kg (p 0.001).[27] The 5:2 intermittent fasting procedure should be used in conjunction with a 600 kcal/day calorie restriction in order to lose weight.[28] Moreover, the period of intermittent fasting intervention in this study lasted for eight weeks, it is possible causes IL-6 levels have not yet yielded statistically meaningful findings. It has been suggested that major changes in IL-6 levels need at least six months of 5:2 intermittent fasting.[29]

This study was the first study in Indonesia to investigate the effect of 5:2 intermittent fasting on IL-6 levels in obese male employees. Although there was a IL-6 level reduction trend in the intermittent fasting group, but it was not significant compared to the non-fasting group.. Future research is needed to analyze several factors affecting IL-6 levels and to measure other inflammatory cytokines in 5:2 intermittent fasting group with a longer intervention period.

Conclusion

Intermittent fasting 5:2 for eight weeks tend to reduce IL-6 levels however it was not significant.

Conflict of interest

There is no conflict of interest in the whole process of this research.

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