

## Original Article

# The role of omega-3/omega-6 ratio on appetite in pulmonary multidrugs resistant tuberculosis

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## ABSTRACT

**Introduction:** TNF- $\alpha$  levels, a pro-inflammatory cytokines which can suppress appetite, were discovered much higher in MDR-TB compared to drug-sensitive TB. Research on the  $\omega$ -3/ $\omega$ -6 PUFAs intake which can support appetite in patients with MDR-TB has never been done. This study was conducted to see if there was a relationship between  $\omega$ -3/ $\omega$ -6 PUFAs intake ratio and appetite mediated by TNF- $\alpha$  in pulmonary MDR-TB.

**Methods:** This cross-sectional study was conducted on 46 adult male and female with MDR-TB who were undergoing intensive phase therapy. Data were collected through questionnaires, 1x24 hours food recall, anthropometric measurements, 100 mm visual analog scale of appetite and venous blood collection.

**Results:** Correlation analysis used pearson and spearman test. The ratio of  $\omega$ -3/ $\omega$ -6 PUFAs intake  $0.11\pm 0.05$ , median value of TNF- $\alpha$   $7,49(1,66-447,62)$  pg/ml and average of appetite  $58,72\pm 26,7$ . There was no relationship between  $\omega$ -3/ $\omega$ -6 PUFAs intake ratio and TNF- $\alpha$  ( $r=0,016$ ;  $p=0,91$ ), likewise between  $\omega$ -3/ $\omega$ -6 PUFAs intake ratio with appetite ( $r=-0,1$ ;  $p=0,54$ ), but there was relationship between TNF- $\alpha$  and appetite ( $r=0,031$ ;  $p=0,04$ ).

**Conclusion:** There was no relationship between  $\omega$ -3/ $\omega$ -6 PUFAs intake ratio with TNF- $\alpha$  and appetite in pulmonary MDR-TB. However, there was a relationship between TNF- $\alpha$  and appetite. To the best of our knowledge, this is the first study of which determined the correlation between  $\omega$ -3/ $\omega$ -6 PUFAs intake ratio and appetite in pulmonary MDR-TB.

**Keywords:** TNF- $\alpha$ , MDR-TB,  $\omega$ -3,  $\omega$ -6, appetite

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## INTRODUCTION

One of the top ten causes of death in the world is tuberculosis (TB). The World Health Organization (WHO) has determine TB as a global emergency<sup>1</sup>. Around 20% of tuberculosis strains are resistant to at least one of anti-TB drug. There were 465,000 cases of rifampisin-resistant TB (RR-TB) in 2019, of which 78% had developed into multidrugs resistant TB (MDR-TB).<sup>2</sup> Indonesia is one of the 20 countries with the highest MDR-TB cases. WHO estimates that there are around 24,000 MDR-TB cases per year in Indonesia, where West Java

is the province with the most MDR-TB cases, there were 1,566 new cases in 2018 and 2,073 cases in 2019.<sup>3</sup>

TB disease can cause malnutrition due to metabolic increase and decrease appetite.<sup>4</sup> TB patients usually show malnutrition.<sup>5</sup> Previous study stated that primary factors associated with poor treatment outcomes for MDR-TB patients are age (> 60 years old), body weight ( $\leq$  50 kg), with cavitary disease or hemoptysis symptoms and treatment irregularity.<sup>6</sup> The inflammatory process in TB leads to increase production of interleukin (IL) -1, IL-6, tumor necrosis factor-alpha (TNF- $\alpha$ ) and malondialdehyde (MDA). The increase in TNF- $\alpha$  is associate with anorexia.<sup>7</sup> A study reported that levels of interferon gamma (IFN- $\gamma$ ) and TNF- $\alpha$  were discovered to be higher in MDR-TB patients compared with drug-sensitive TB patients.<sup>8</sup>

In a randomized control trial (RCT), the administration of eicosapentaenoic acid (EPA), which is a group of omega-3 ( $\omega$ -3) polyunsaturated fatty acids (PUFAs), was found to be associated with an increase in appetite in healthy adults. In anorexia-cachexia syndrome, it reduces the production of c-reactive protein (CRP), IL-6 and TNF- $\alpha$ . In addition, it also inhibits the ubiquitin-proteasome pathway in muscle loss, so insulin sensitivity increases, it improves protein and calorie intake. In another study, EPA supplementation could improve and cure anorexia nervosa in young patients. Oral EPA supplementation in patients with non-small cell lung cancer can actually increase eating intake, restore appetite and increase lean body mass compared to control. The EPA dose given is 1 g once daily to 1 g twice daily.<sup>9</sup> Pizzini et al.<sup>10</sup> reported that  $\omega$ -3 PUFAs can limit and improve the inflammatory process in the body of people with chronic obstructive pulmonary disease (COPD), including lowering TNF- $\alpha$  levels. The properties of  $\omega$ -3 and omega-6 ( $\omega$ -6) PUFAs have opposite ways of working. EPA and DHA which are the  $\omega$ -3 PUFAs group produce specialized proresolving lipid autacoid mediators (SPMs), such as resolvins that can reduce inflammation, while linoleic acid (LA) and arachidonic acid (ARA) which are groups of  $\omega$ -6 PUFAs, increase inflammation and proliferation of fat cells.<sup>11</sup>

Research on the effect of  $\omega$ -3 PUFAs on reducing inflammation and appetite has never been carried out in people with MDR-TB, therefore, it is necessary to conduct research on the relationship between PUFAs consumption ratios of  $\omega$ -3/ $\omega$ -6 to appetite which is mediated by TNF- $\alpha$  in people with MDR-TB, which was conducted at Dr. M. Goenawan Partowidigdo Lung Hospital Bogor, West Java, Indonesia.

## **METHODS**

### **Study Participants**

From December 2019 to March 2020, a cross-sectional study with consecutive sampling method was done at Dr. M. Goenawan Partowidigdo Lung Hospital (RSPG) Bogor, West Java, Indonesia. Adults, male and female aged 19 - 49 years old, diagnosed with MDR-TB and undergoing intensive phase therapy of MDR-TB. Subjects with history of autoimmune and immunocompromised diseases; taking  $\omega$ -3 and  $\omega$ -6 PUFAs supplement; pregnant or breastfeeding were not allowed to participate. Prior to recruitment, written consent form was received from participants. Subjects also completed a socio-demographic questionnaire and 100 mm visual analog scale of appetite. The Ethical Committee Faculty of Medicine, University of Indonesia, Jakarta, approved the study procedure (No. KET-1317/UN2.F1/ETIK/PPM.00.02/2019).

### **Dietary Intake**

For the study, a semi-quantitative Food Frequency Questionnaire (FFQ) was used to collect dietary consumption of  $\omega$ -3 and  $\omega$ -6 PUFAs during the previous month. For total energy, fat intake and protein intake used 1x24 hours food recall. Dietary consumption was determined using food composition data from local and Asian countries.

### **Anthropometric Measurement**

The measurement of height was carried out with the aid of a height measuring board (ShorrBoard, Olney, USA), weight and body composition measurement carried out by using Tanita type SC-330 body composition analyzer (Tanita, Tokyo, Japan) for body weight.

### **Laboratory Analysis**

Venous blood sample were drawn and centrifuged at 3000 rpm for 10 minutes, the serum was then refrigerated at  $-20^{\circ}\text{C}$  until it was tested at the Department of Biochemistry and Molecular Biology Laboratory, Faculty of Medicine, University of Indonesia, Jakarta. Enzyme-Linked Immunosorbent Assay (ELISA) kit (Elabscience, USA) was used to measured TNF- $\alpha$  level.

## Data Analysis

The Statistical Package for the Social Sciences version 20 (SPSS Ins, Chicago, IL, USA) was used to analyze data. Dietary intake were evaluated using NutriSurvey 2007 (Germany). The normality data of subjects characteristics, dietary intake, TNF- $\alpha$  serum levels and appetite were assessed using kolmogorov-smirnov test. Spearman correlation test was applied to evaluate relationship between  $\omega$ -3/ $\omega$ -6 PUFAs ratio with TNF- $\alpha$ . Pearson correlation test was applied to determine relationship between TNF- $\alpha$  and appetite, and relationship between  $\omega$ -3/ $\omega$ -6 PUFAs ratio with appetite. If  $p < 0.05$ , the association is considered significant.

## RESULTS

Forty-six adult diagnosed with MDR-TB and currently undergoing intensive phase of therapy were participated, The mean age of participants was  $34.26 \pm 11.64$  years old with female-gender majority. Most of subjects had low to middle educational background and had a low income level. Fat free mass (FFM) average were  $37.04 \pm 7.2$  kg, most of subjects had a low body weight and most of them were former active smoker, as seen in Table 1.

**Table 1.** Subject characteristics

Parameter (n=46)	n (%)	Average/median
Age (year)		$34.26 \pm 11.64$
Gender		
Male	21(45.7%)	
Female	25(54.3%)	
Education level		
Low	26(56.5%)	
Middle	16 (34.8%)	
High	4 (8.7%)	
Income level		
Low	40(87%)	
Enough	6(13%)	
FFM (kg)		$37.04 \pm 7.2$
BMI ( $\text{kg}/\text{m}^2$ )		$17.96 \pm 3.75$
Nutritional status		
Low	31(67.4)	
Normal	9(19.6)	
Overweight	4(8.7)	
Obese I	2(4.3)	
Smoking history		
Former active smoker	24(52.2)	
Not active smoker	1(2.2)	
Passive smoker	13(28.3)	
Not passive smoker	8(17.4)	

Table 2. shows that the majority of the individuals did not consume enough total energy and total protein to meet the Institute of Medicine Dietary Reference Intake (DRI). On the other hand, the majority of the participants had enough total fat intake. The median intake of  $\omega$ -3 PUFAs were 0.13(0.00-1.38) g/day and  $\omega$ -6 PUFAs was 1.09 (0.04-10.38) g/day. This study found that the average  $\omega$ -3/ $\omega$ -6 PUFAs ratio was 0.11 $\pm$ 0.05. The median of TNF- $\alpha$  serum level was 7.49(1.66-447.62) pg/mL. The average of 100 mm VAS score of appetite was 58.72 $\pm$ 26.7, most of the subjects experienced anorexia.

**Table 2.** Distribution of Dietary Intakes

Dietary intake (n=46)	n(%)	Average/median
Total energy (kcal/day)		1499.88 $\pm$ 549.32
Level of energy		
Low	24(52.2)	
High	22(47.8)	
Total fat (g/day)		52.12 $\pm$ 34.61
Level of fat		
Low	22(47.8)	
High	24(52.2)	
Total protein (g/day)		51.63 $\pm$ 26.68
Level of protein		
Low	32(69.6)	
High	14(30.4)	
$\omega$ -3 (g/day)		0.13(0.00-1.38)
Level of $\omega$ -3		
Low	45(97.8)	
High	1(2.2)	
$\omega$ -6 (g/day)		1.09(0.04-10.38)
Level of $\omega$ -6		
Low	46(100)	
High	0(0)	
$\omega$ -3/ $\omega$ -6		0.11 $\pm$ 0.05
TNF- $\alpha$ (pg/ml)		7.49(1.66-447.62)
Appetite		58.72 $\pm$ 26.7
Anorexia	29(63)	
Not anorexia	17(37)	

The Spearman test was performed to see the correlation between  $\omega$ -3/ $\omega$ -6 PUFAs intake ratio with TNF- $\alpha$  level, between TNF- $\alpha$  level and  $\omega$ -3/ $\omega$ -6 PUFAs ratio with Appetite. Table 3. shows that there was no correlation between  $\omega$ -3/ $\omega$ -6 PUFAs intake ratio with TNF- $\alpha$  level, also between  $\omega$ -3/ $\omega$ -6 PUFAs intake ratio with appetite. TNF- $\alpha$  level and appetite had significant correlation.

**Table 3.** Correlation between variables

Variables	R coefficient *	p value**
$\omega$ -3/ $\omega$ -6 PUFAs and TNF- $\alpha$	0.016	0.91
TNF- $\alpha$ and appetite	0.031	0.04
$\omega$ -3/ $\omega$ -6 PUFAs and appetite	-0.1	0.54

Notes: \* R >0.7 very strong correlation; 0.4-0.69 strong relationship; 0.3-0.39 moderate relationship; 0.2-0.29 weak relationship; 0.01-0.19 negligible relationship. \*\*statistical significant (p<0.05)

In this study, an additional analysis was carried out in the form of tests between age, body mass index (BMI), FFM, total fat intake and total energy with appetite. Spearman correlation test was conducted on gender, education level, income level and smoking history. The results of the correlation test indicated that there was a link between the FFM and appetite (r=0.33; p=0.025), total energy also showed a correlation with appetite (r=0.37; p=0.01), intake of  $\omega$ -3 PUFAs and appetite (r=0.33; p=0.03), intake of  $\omega$ -6 PUFAs and appetite (r=0.34; p=0.02). Although the analysis found several variables that had a significant p value, the r value (correlation coefficient) was weak.

## DISCUSSION

This study found that most MDR-TB patients at RSPG consumed  $\omega$ -3 and  $\omega$ -6 PUFAs under DRI (97.8% and 100%), although most of the total fat intake was sufficient (52.2%). The adequacy of the total fat intake is likely due to the fact that most of the food consumed is fried and sauteed food, while the lack of intake amounts of  $\omega$ -3 and  $\omega$ -6 PUFAs, is likely due to the fact that most of the subjects experienced anorexia (63%), as well as having low income and education (56.5% and 87%). Van Der Meij, et al.<sup>12</sup> conducted a study on a healthy population in the United States, the study reported that decrease appetite has a significant relationship with female, black skin, smokers, low educated and low-income individuals (p<0.05).

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This study also found that there was no correlation between  $\omega$ -3/ $\omega$ -6 PUFAs ratio and serum TNF- $\alpha$  level in pulmonary MDR-TB patients at RSPG. From previous research, administration of EPA and DHA decreases the production of pro-inflammatory cytokines TNF- $\alpha$ , IL-1 and IL-6, as well as increases the concentration of IL-10 known as anti-inflammatory cytokines.<sup>13</sup> EPA and DHA have been shown to inhibit TNF- $\alpha$ , cytokine which mostly produced in the infection process by Mtb. This mechanism allows to reduce anorexia and decrease body weight. Conversely, the study by Hu, et al.<sup>14</sup> stated that there is no significant difference in TNF- $\alpha$  level between subjects who consumed  $\omega$ -3 PUFAs and controls. His research reported that  $\omega$ -3 PUFAs supplementation has no significant effect on serum IL-6, TNF- $\alpha$  and CRP levels reduction in CKD patients who are or are not on dialysis. Therefore, research on the effect of  $\omega$ -3 PUFAs on TNF- $\alpha$  level in MDR-TB patient still requires further research.

This study found that there was no correlation between serum TNF- $\alpha$  levels and appetite in pulmonary MDR-TB patients. This may be because cytokine testing was only performed on TNF- $\alpha$ , whereas there are several other cytokines that promote inflammation not checked, such as IL-1, IL-2, IL-6, IL-8 and IFN- $\gamma$  which are known to suppress appetite. In addition, the TNF- $\alpha$  measurement was only carried out once in the intensive treatment phase and not carried out in the advanced treatment phase, this allows for differences in results. TNF- $\alpha$  levels will decrease with progression of treatment, so there is no comparison in the follow-up phase. Insulin resistance and sensation of fullness in the hypothalamic anorexia centers are induced by IL-1 and TNF- $\alpha$ .<sup>15</sup>

In this study, there was no correlation between the  $\omega$ -3/ $\omega$ -6 PUFAs consumption ratio and appetite in pulmonary MDR-TB patients. This research is the first to establish the correlation between the  $\omega$ -3/ $\omega$ -6 PUFAs consumption ratio and appetite in patients with MDR-TB. Sari, et al.<sup>16</sup> reported the  $\omega$ -3/ $\omega$ -6 PUFAs consumption ratio in 54 healthy women who worked in Semarang city government offices was 1:16. A clinical study reported that administering EPA and DHA of 600 mg/d to 3.6 g/d can maintain and increase body weight, as well as improve and minimize lean body mass loss.<sup>17</sup> In contrast to Simopoulos, et al.<sup>18</sup> who conducted research on  $\omega$ -3 as a weight-lowering agent, this study states that a high intake of  $\omega$ -6 PUFAs, and a high ratio consumption of  $\omega$ -6/ $\omega$ -3 PUFAs is linked to western gain, while  $\omega$ -3 PUFAs reduce the risk of gaining weight. Leptin and insulin resistance in cells are increase by a diet high in  $\omega$ -6 PUFAs, while  $\omega$ -3 PUFAs maintain homeostasis and can reduce body weight.



## LIMITATION

This study only measured TNF- $\alpha$ , whereas there are other cytokines that can affect appetite. Data collection of  $\omega$ -3 and  $\omega$ -6 PUFAs intake was only carried out by 1x24 hours recall method. There is still no gold standard instrument to assess appetite in people with pulmonary MDR-TB.

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## CONCLUSION

There was no relationship between  $\omega$ -3/ $\omega$ -6 PUFAs intake ratio with TNF- $\alpha$  and appetite in pulmonary MDR-TB. However, there was a relationship between TNF- $\alpha$  and appetite.

A prospective cohort study is recommended to know better the relationship between  $\omega$ -3/ $\omega$ -6 PUFAs intake ratio with appetite. Further studies could be done to enrich the  $\omega$ -3 and  $\omega$ -6 PUFAs content in the database of Indonesian foods and also studies in specific gender. Studies measuring  $\omega$ -3 and  $\omega$ -6 PUFAs concentrations in erythrocytes membrane to see the  $\omega$ -3/ $\omega$ -6 PUFAs ratio more objectively are also warranted. The authors suggest a study of cytokines and other factors that can affect appetite in MDR-TB for future research.

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## CONFLICT OF INTEREST

In this study, the authors have no competing interests.

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## REFERENCES

1. Global Tuberculosis Report 2018 (cited 2019 Januari 10). Available from: URL: [https://www.who.int/tb/publications/global\\_report/en/](https://www.who.int/tb/publications/global_report/en/).
2. Weng T, Sun F, Li Y, et al. Refining MDR-TB treatment regimens for ultra short therapy (TB-TRUST): study protocol for a randomized controlled trial. *BMC infect dis.* 2021;21:183. doi:10.1186/s12879-021-05870-w

3. Soeroto AY, Pratiwi C, Santoso P, et al. Factors affecting outcome of longer regimen multidrug-resistant tuberculosis treatment in West Java Indonesia: A retrospective cohort study. *PLoS One*. 2021 Feb 8; 16(2): e0246284. doi: [10.1371/journal.pone.0246284](https://doi.org/10.1371/journal.pone.0246284)
4. Grobler L, Nagpal S, Sudarsanam TD, Sinclair D. Nutritional supplements for people being treated for active tuberculosis. *The Cochrane Library*. 2016 Jun;2016(6):CD006086. doi:10.1002/14651858.CD006086.pub4
5. Moraes ML, Ramalho DM, Delogo KN, et al. Association between serum selenium level and conversion of bacteriological tests during antituberculosis treatment. *J Bras Pneumol*. 2014 May-Jun;40(3):269-278. doi:10.1590/S1806-37132014000300010
6. Zhang, M. W., Zhou, L., Zhang, Y., Chen, B., Peng, Y., Wang, F., Liu, Z. W., Wang, X. M., & Chen, S. H. (2021). Treatment outcomes of patients with multidrug and extensively drug-resistant tuberculosis in Zhejiang, China. *European journal of medical research*, 26(1), 31. doi: <https://doi.org/10.1186/s40001-021-00502-0>
7. Song T, Li LJ, Liu JL, Geng SJ. Study on the relationship between changes of immune cells and TNF- $\alpha$  in peripheral blood of patients with multidrug-resistant and extensively drug-resistant tuberculosis. *Eur rev med pharmacol sci*. 2018;22(4):1061-1065. doi:10.26355/eurrev\_201802\_14389
8. Basingnaa A, Antwi-Baffour S, Nkansah DO, Afutu E, Owusu E. Plasma Levels of Cytokines (IL-10, IFN-gamma and TNF-alpha) in Multidrug Resistant Tuberculosis and Drug Responsive Tuberculosis Patients in Ghana. *Diseases*. 2018;7(1). doi:10.3390/diseases7010002
9. Hariyanto TI, Kurniawan A. Appetite problem in cancer patients: Pathophysiology, diagnosis, and treatment. *Cancer Treat Res Commun*. 2021; 27: 100336. doi: [10.1016/j.ctarc.2021.100336](https://doi.org/10.1016/j.ctarc.2021.100336)
10. Pizzini A, Lunger L, Sonnweber T, Weiss G, Tancevski I. The Role of  $\omega$ -3 PUFAs in the Setting of Coronary Artery Disease and COPD: A Review. *Nutrients*. 2018;10(12):1864. doi:10.3390/nu10121864
11. Simopoulos AP. Genetic Variation, Diet, Inflammation, and the Risk for COVID-19. *Lifestyle Genom*. 2021;14(2):37-42. doi:10.1159/000513886
12. Van der Meij BS, Wijnhoven HA, Lee JS, et al. Poor appetite and dietary intake in community-dwelling older adults. *Journal of the American Geriatrics Society*. 2017;65(10):2190-2197. doi: 10.1111/jgs.15017. Epub 2017 Jul 26
13. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans*. 2017;45(5):1105-1115. doi:10.1042/BST20160474
14. Hu C, Yang M, Zhu X, et al. Effects of  $\omega$ -3 PUFAs on markers of inflammation in patients with chronic kidney disease: A controversial issue. *Therapeutic Apheresis and Dialysis*. 2018;22(2):124-132. doi:10.1111/1744-9987.12611
15. Avila-Carrasco L, Pavone MA, González E, et al. Abnormalities in Glucose Metabolism, Appetite-Related Peptide Release, and Pro-inflammatory Cytokines Play a Central Role in Appetite Disorders in Peritoneal Dialysis. *Front Physiol*. 2019;10:630. Published 2019 May 28. doi:10.3389/fphys.2019.00630
16. Sari ML, Probosari E, Wijayanti HS. Hubungan Asupan Asam Lemak  $\omega$ -3 dan  $\omega$ -6 dengan Tekanan Darah Wanita Usia 30–50 tahun, Diponegoro University; 2017. doi:10.14710/jnc.v6i4.18668
17. Mattox TW. Cancer Cachexia: Cause, Diagnosis, and Treatment. *Nutr Clin Pract*. 2017;32(5):599-606. doi:10.1177/0884533617722986
18. Simopoulos A. An increase in the  $\omega$ -6/ $\omega$ -3 PUFAs ratio increases the risk for obesity. *Nutrients* 8: 128. In:2016. doi:10.3390/nu8030128

