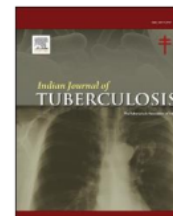


# Leptin levels in childhood tuberculosis and its correlation with body mass index, IFN-g, and TNF-a in an Indonesian population

*By Moh Syarofil Anam*

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Original article

## Leptin levels in childhood tuberculosis and its correlation with body mass index, IFN- $\gamma$ , and TNF- $\alpha$ in an Indonesian population

Moh Syarofil Anam <sup>a,\*</sup>, Maria Mexitalia <sup>a,b</sup>, Binar Panunggal <sup>c</sup>,  
Magdalena Sidhartani <sup>a</sup>, Banundari Rachmawati <sup>d</sup>,  
Hertanto Wahyu Subagio <sup>e</sup>

<sup>a</sup> Department of Child Health, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

<sup>b</sup> Kariadi Hospital, Semarang, Indonesia

<sup>c</sup> Department of Nutrition, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

<sup>d</sup> Department of Clinical Pathology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

<sup>e</sup> Department of Clinical Nutrition, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

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## ABSTRACT

**Background:** Leptin plays a key role in the regulation of energy and inflammation in tuberculosis (TB). However, its correlation in children with TB remains unclear. Therefore, this study aimed to evaluate the correlations between body mass index, IFN- $\gamma$ , TNF- $\alpha$ , and leptin levels in children with TB.

**Methods:** This was a cross-sectional study of children aged 2–14 years with TB. Sputum examination, chest radiography, and tuberculin skin test findings and clinical symptoms were considered for TB diagnosis. Data on body weight; height; mid-upper arm circumference (MUAC); body mass index (BMI); food intake; and IFN- $\gamma$ , TNF- $\alpha$ , and leptin levels were collected and analyzed.

**Results:** Of the 64 diagnosed TB subjects, 2 subjects had positive bacteriological results. The median age was 6 (2–14) years, body weight was 17.7 (9.45–55) kg, height was 114  $\pm$  21.46 cm, and Z score BMI was  $-0.85 \pm 1.14$  kg/m<sup>2</sup>. Malnourished was observed in 17.2% of the subjects. The median calorie intake was 1448.5 (676–4674) kcal, carbohydrate intake was 182.5 (63–558) g, protein intake was 57.9 (15.8–191.0) g, and fat intake was 81.6 (23.6–594.1) g. The median leptin level was 1.2 (0.2–59) ng/mL, IFN- $\gamma$  was 2.5 (0.9–161) pg/mL, and TNF- $\alpha$  was 13.0 (5.7–356) pg/mL. Correlations were observed between leptin and MUAC ( $r = 0.251$ ,  $p = 0.02$ ), Z score ( $r = 0.453$ ,  $p = 0.00$ ), and IFN- $\gamma$  ( $r = 0.295$ ,  $p = 0.018$ ).

**Conclusion:** There were positive correlations between BMI and leptin levels, whereas IFN- $\gamma$  and MUAC showed weak correlations.

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\* Corresponding author. Fax: +62248414296, Tel.: +6281367428988.

E-mail address: [msanam77@fk.undip.ac.id](mailto:msanam77@fk.undip.ac.id) (M.S. Anam).

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## 1. Introduction

Tuberculosis (TB) is still a considerable problem among children in developing countries. The incidence of TB worldwide is estimated at 10 million cases, 12% of which are diagnosed in children.<sup>1</sup> In 2019, the incidence of TB in Indonesia was 845,000 cases, denoting Indonesia as the country with the second highest TB incidence globally; moreover, in 2015, the proportion of pediatric TB cases in Indonesia compared with the total TB cases in Indonesia was 9%.<sup>1,2</sup>

Malnutrition is reportedly an important problem in developing countries with high TB morbidity rates and is associated with 2.2 million deaths annually.<sup>3</sup> TB is often accompanied by malnutrition, which can lead to inadequate treatment response and affect disease outcomes.<sup>4,5</sup> Malnutrition in children can cause an inadequate immune response, including host defense mechanisms, cellular immunity, and impaired regulation of proinflammatory or anti-inflammatory mediators, which are needed in the healing process.<sup>4</sup>

Leptin, a hormone produced by adipocytes, plays an important role in malnutrition in children.<sup>6</sup> Leptin is a mediator involved in the complex relationship between TB, nutritional status, and host immune response; thus, it is possible that leptin may also play an important role in regulating food intake, energy consumption, and controlling body weight.<sup>7</sup> Leptin has an important function in the regulation of the body's immune system by activating macrophages and other immune cells to secrete Th-1-mediated proinflammatory cytokines.<sup>8</sup> Children with TB have been observed to have low leptin levels,<sup>9</sup> which can be detrimental to the host immune system because it causes the cellular response of stimulating macrophages to secrete Th-1, including TNF- $\alpha$  and IFN- $\gamma$ , which play an important role in TB infection.<sup>10,11</sup> Neverthe-

less, the relationship between leptin, IFN- $\gamma$ , and TNF- $\alpha$  in pediatric patients with TB is not yet fully understood.

Therefore, this study aimed to assess the correlation between nutritional status, TNF- $\alpha$ , IFN- $\gamma$ , and leptin in pediatric patients with TB and nutrition-related variables such as weight, height, mid upper arm circumference, body mass index, calorie intake, carbohydrates, protein, and fat.

## 2. Methods

A cross-sectional analysis was conducted among children aged 2 to 14 years with pulmonary TB who visited the Lung Community Health Centre in Semarang, Central Java, Indonesia, between January 2020 and January 2021. Consecutive sampling methods were used for enrollment. Ethical clearance was provided by the Ethics committee of Diponegoro University (384/EC/KEPK/FK-Undip/VIII/2019) and written informed consent was obtained from all subjects prior to study participant.

The eligibility criteria were as follows: children presenting with symptoms of pulmonary TB, including chronic fever, decreased body weight, chronic cough, and malaise; children who underwent the tuberculin skin test (TST) and chest radiography; and children with sputum specimens from spontaneous expectorate or with induction sputum (that has

been collected whenever possible). TST was performed by trained health workers with PPD RT 23 2 TU from the Staten Institute in Denmark, with an injection of 0.1 mL while sitting on a Volair arm chair. An induration  $\geq 10$  mm after 72 h was considered a positive result by trained health workers. A radiologist and a clinician performed chest radiography according to the Union Against Tuberculosis and Lung Disease guideline.<sup>12</sup> Children diagnosed with TB according to the consensus of experts on the clinical classification of TB, with only *confirmed* and *probable* cases considered, were included.<sup>13</sup> The exclusion criteria were as follows: (1) extrapulmonary TB and (2) presence of comorbidities such as acute infection, human deficiency virus (HIV), malignancy, and other chronic diseases.

Body weight was measured using a SECA® digital weighing scale (Seca, Deutschland) with an accuracy of 10 g, height was measured using a stadiometer with an accuracy of 1 mm, nutritional status was expressed through the BMI Z score according to WHO standards, and wellnourished was defined as a Z score ranging from  $-2$  SD to 2 SD. Nutritional intake was measured using a semi-quantitative food frequency questionnaire by trained enumerators, and the results were analyzed using a Nutrisurvey® 2007 (EBISpro, Germany) to obtain results of calorie, protein, carbohydrate, and fat intake. Four milliliters of blood samples were taken in the morning and centrifuged to obtain the plasma contents. Measurement of laboratory parameters was carried out at the "GAKY" laboratory, Diponegoro University BSF level 2, using an enzyme linked immunosorbent assay (ELISA), with reagents for IFN- $\gamma$  using the human IFN- $\gamma$  ELISA kit from Elabscience™, human TNF- $\alpha$  from Elabscience™, and reagent leptin for the ELISA kit (Diagnostic Biochem Canada Inc., Ontario, Canada). The normal values based on the kit for each parameter were as follows: IFN- $\gamma$ ,  $<2.0$  pg/mL; TNF- $\alpha$ ,  $<15.6$  pg/mL; and leptin,  $3.7 \times 10^{11.1}$  ng/mL (for females), and  $2.0 \times 10^{5.6}$  ng/mL (for males).

SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data are presented as mean  $\pm$  standard deviation and median (range), according to data distribution. Correlation tests were conducted using Spearman's rank test. A p value  $< 0.05$  was considered significant.

## 3. Results

In total, the data of 64 children diagnosed with TB were analyzed. Forty children were subjected to bacteriological examination, with two (5%) positive results of Xpert® MTB/RIF assay. As many as 24 children could not be subjected to bacteriological examination because they were unable to excrete sputum and refused sputum induction. None of the study subjects tested positive for HIV during a rapid examination. The characteristics of the study participants are presented in Table 1. The TB diagnosis status among the study subjects was 95% probable or clinical TB. The most common clinical symptom was weight loss of 75%, followed by a history of contact with adult patients with TB in 57.8% of cases.

Nutritional status examination found that 17.2% of all study subjects were malnourished, with a BMI Z score of  $-0.81 \pm 1.14$  SD. The median body weight of the research

Table 1 e Characteristics of the study subjects.

Variable	Subjects (%)
Age, years (median, [range])	6 (2e14)
Sex	
Boy	33 (51.6%)
Girl	31 (48.4%)
History of contact	
Present	37 (57.8%)
Absent	27 (42.2%)
Symptoms	
Fever	2/64 (3.1%)
Cough	10/64 (15.6%)
Decreased body weight	48/64 (75%)
Malaise/decreased activity	8/64 (12.5%)
Lymph node enlargement	13/64 (20.3%)
Tuberculin result	
>10 mm	59 (92.2%)
<10 mm	5 (7.8%)
Chest radiography finding	
Hilar enlargement	51/64 (79.7%)
Infiltrate	30/64 (46.9%)
Both	29/64 (45.3%)
Diagnosis of tuberculosis	
Confirmed	2/64
Probable	62/64

Symptoms defined as chronic unremitting with standard treatment other than anti-tuberculosis drugs, such as anti-pyretic for fever and salbutamol for cough, with symptoms lasting at least 2 weeks for fever and cough, and 1 month for other symptoms.

subjects was 17.7 (9.45e55) kg, while the mean height was 114.5 ± 21.46 cm. Fifty of 64 subjects showed wellnourished, 8/64 were mild-moderate malnourished, 4/64 were severe malnourished, and 2/64 were overweight. Moreover, 6/64 subjects in this study were stunted. Based on the mid-upper

Table 2 e Nutritional parameters of the subjects.

Parameter	Subjects (n ¼ 64)
Weight, kg	17.7 (9.45e55)
Height, cm	114 ± 21.46
HAZ (SD)	−1.3 (−4.4e3.13)
Z score BMI	−0.85 ± 1.14
Mid-upper arm circumferences	15.9 (11.5e26.4)
Nutritional status	52 (81.3%)
Wellnourished	11 (17.2%)
Malnourished	
Calorie intake (kcal)	1448.5 (676e4674)
Carbohydrates intake (g)	182.5 (63e558)
Protein intake (g)	57.9 (15.8e191.0)
Fat intake (g)	81.6 (23.6e594.1)
Leptin level, ng/mL	1.2 (0.2e59)
IFN-g level, pg/mL	2.5 (0.9e161)
TNF-a level, pg/mL	13.0 (5.7e356)

Values are presented as number (%) or mean (standard deviation) or median (interquartile range).

TNF, tumor necrosis factor; IFN, interferon; kg, kilogram; cm, centimeter; HAZ, z score height for age; BMI, body mass index; MUAMC, mid-upper arm circumference; kcal, kilocalories; g, gram; pg/mL, picogram/milliliter.

arm circumference (MUAC) values, 2/64 subjects had MUAC <11.5 cm. The differences between leptin levels and nutrient intake of calories, proteins, carbohydrates, and fats are shown in Table 2 and Fig. 1.

According to the studied laboratory parameters, high IFN-g values were observed in 35/64 (54.6%) subjects, with a median value of 2.5 (0.9e161) pg/mL. Increased TNF-a was observed in 20/64 (31%) subjects, with a median value of 13.0 (5.7e356) pg/mL, whereas low leptin levels were found in 45/64 (70.3%) subjects, with a median value of 1.2 (0.2e59) ng/mL. Subjects with symptoms of decreased body weight also showed a lower leptin median value of 0.95 (0.4e59.0) ng/mL, compared with 3.3 (0.4e59.0) ng/mL in those without weight loss symptoms, with a significance value of  $p \leq 0.021$ ; however, there was no difference in nutritional status between these two groups.

Table 3 presents the correlation between the nutritional parameters, IFN-g, TNF-a, and leptin.

#### 4. Discussion

TB in children has been associated with mild clinical conditions. In our study, only 5% of the cases were bacteriologically positive or showed large numbers of bacteria, but we did not perform culture examination as a gold standard for diagnosing TB for the reason that this is not routinely done in our setting. This was related to some of the subjects' inability to produce good sputum, and parental refusal to induce sputum or undergo gastric lavage procedures. Our research subjects also showed relatively mild thoracic radiography results compared with the thoracic results of adult patients with TB, and the more dominant clinical symptoms were weight loss symptoms, rather than respiratory symptoms. This is because our research subjects were patients with TB in the community or were children coming to first-level healthcare facilities, such that the resulting clinical vignette is at an early stage of disease progression, compared with the pediatric TB population in the hospital setting, which is dominated by severe forms of TB, including extrapulmonary TB.<sup>14</sup>

Malnutrition in childhood TB has long been a concern of experts because it can affect disease outcomes and is associated with high mortality rates.<sup>3e5</sup> In this study, we found through the nutritional status of the enrolled patients that only 17.5% had malnutrition. However, the rate of weight loss, which is the initial stage of malnutrition, was observed in 75% of cases. Leptin reportedly has a strong role in the association of malnutrition and inflammation in pediatric TB, and low leptin levels were observed in 70% of our study subjects, similar to previous studies.<sup>7,9</sup> A meta-analysis by Ye et al. found evidence that leptin levels in patients with TB were lower than that in control subjects.<sup>15</sup> Our study supports these findings, as we similarly observed low leptin levels among our subjects. In contrast, Zheng et al.<sup>16</sup> obtained contrasting results, with higher leptin levels observed in adult patients with TB than in healthy controls. This striking difference may have occurred because leptin is not only regulated by energy regulation but also by inflammatory processes, which have been shown to increase in adult patients with TB.

Interestingly, the leptin levels in our study subjects were found to be lower among those who showed symptoms of



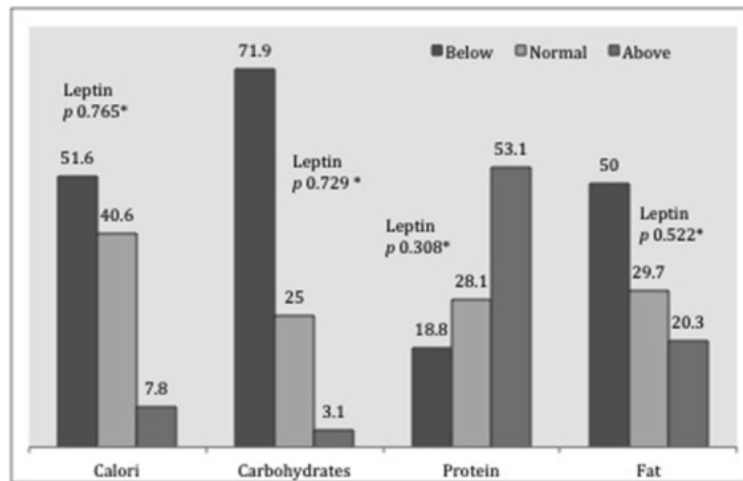


Fig. 1 e Correlation between nutritional intake percentage and leptin level. The data show low intake of calories, carbohydrates, and fat among subjects; however, protein intake was above the normal requirements (the data on nutritional intake values are presented in percentage (%), according to the Indonesian Dietary Recommendation). There are no differences in leptin levels between the groups. (\*) The chi-square test used to compare between groups;  $p < 0.05$  indicates statistical significance.

weight loss than in those with malnutrition (however, the difference was not significant), suggesting that the weight loss process is related to malnutrition and has more influence on leptin levels than nutritional status, which is more indicative of chronic conditions. Nutritional intake is also known to be associated with leptin levels,<sup>17</sup> and dietary intake decreases in low leptin conditions; however, our current study was not able to prove that nutritional intake was related to leptin levels, perhaps because our subjects were patients who were diagnosed early. A decrease in nutritional intake that occurs owing to low levels of leptin is a process that occurs after the patient is already deemed malnourished.<sup>17e19</sup>

Leptin is regulated by the ob gene, with adipocytes as the producers.<sup>18</sup> Circulating leptin in the blood can regulate food intake and nutrient metabolism processes, which in turn will have an impact on nutritional status. Leptin reportedly regulates the processes of gluconeogenesis and gluconeogenesis by regulating blood glucose levels, and leptin levels regulate the balance of nutrient intake.<sup>18,20</sup> In addition to regulating energy intake, leptin can also regulate energy expenditure and, in conditions wherein there are high levels of leptin, it can reduce nutrient intake<sup>21</sup>; nevertheless, this phenomenon is not yet fully understood under the conditions of TB. Moreover, our study could not prove the correlation between leptin levels and other nutritional parameters such as weight, height, MUAC, and nutritional intake, which hence warrants further research.

High levels of inflammatory markers IFN- $\gamma$  and TNF- $\alpha$  have been found in only 54% and 30% of pediatric subjects with TB who showed varying levels of inflammation, respectively, which differs from the theory that under inflammatory conditions, TNF- $\alpha$  and IFN- $\gamma$  work simultaneously in regulating the inflammatory process in patients with TB.<sup>11</sup> This condition may be influenced by the minimal effect of leptin, which contributes in disrupting the regulation of cytokines under conditions of malnourishment.<sup>22</sup> Another theory is that TB in children may have different aspects of inflammatory regulation during each step of the infection process. Proinflammatory cytokines such as IFN- $\gamma$  and TNF- $\alpha$  are associated with leptin through the regulation of macrophage function, wherein leptin not only plays a role in energy balance but also is associated with the regulation of inflammation.<sup>19,22</sup> IFN- $\gamma$  will decrease leptin production; however, TNF- $\alpha$  will increase leptin production through the regulation of adipocytes.<sup>23</sup> Patients with TB experience increased immunological activity in

Table 3 e Correlation between nutritional parameters and leptin levels.

Parameter	Correlation coefficient	p value
Weight	0.236	0.061
Height	0.164	0.195
MUAC	0.251	0.029*
BMI Z score	0.453	0.000*
Energy intake	-0.079	0.534
Carbohydrates intake	-0.064	0.614
Protein intake	-0.090	0.480
Fat intake	0.004	0.975
IFN- $\gamma$	0.295	0.018*
TNF- $\alpha$	0.145	0.252

TNF, tumor necrosis factor; IFN, interferon; BMI, body mass index; MUAC, mid-upper arm circumference.

\*  $p < 0.05$  indicates statistical significance; moderate correlation: correlation coefficient of 0.4e0.6; weak correlation: correlation coefficient of 0.2e0.4; no correlation: correlation coefficient  $< 0.2$  (Spearman correlation rank test).

response to infection; thus, levels of proinflammatory cytokines such as IFN and TNF will be high at the beginning of the infection.<sup>24</sup> The hypothesis is that there is a negative correlation between levels of IFN, TNF, and leptin in patients with TB, in response to the regulation of inflammation. However, previous studies have not been able to prove this hypothesis,<sup>16,25</sup> including our current study, which only found evidence of a weak correlation between IFN- $\gamma$  and leptin. This may be because most previous studies, as well as our study, did not use specific antigen of *Mycobacterium tuberculosis* (for example ESAT-6, CFP-10, or TB 7.7) for stimulating levels of IFN- $\gamma$  and TNF- $\alpha$ . Therefore, further research needs to be conducted using specific levels of IFN- $\gamma$  and TNF- $\alpha$ . In contrast, studies conducted on obese pediatric patients have proven the correlation between proinflammatory cytokine levels and leptin levels.<sup>26</sup> This is owing to the different characteristics of energy regulation and inflammatory activity between obese patients and TB.

Our study has some limitations. We did not use specific inflammation markers of TNF- $\alpha$  and IFN- $\gamma$  for tuberculosis, and 24 of our subjects were unable to receive or refused bacteriological sputum examination. Further research concerning specific inflammation markers and homogeneity of the subjects should be conducted.

In conclusion, our study proved that in pediatric patients with TB, there is a correlation between BMI and leptin levels, a weak correlation between IFN- $\gamma$  and leptin levels, and no correlation between TNF- $\alpha$  and leptin levels.

#### Author's contribution

Conceived and designed study: Anam MS, Mexitalia M, Sidhartani M, Subagio HW.

Performed the study: Anam MS, Mexitalia M, Rachmawati B, Subagio HW.

Analyzed the data: Anam MS, Binar P, Mexitalia M, Subagio HW.

Writing the paper: Anam MS, Sidhartani M.

Approval of final manuscript: all authors.

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#### Conflicts of interest

The authors have none to declare.

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