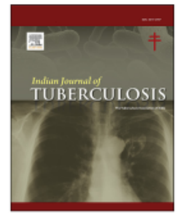
TURNITIN-Leptin

by Moh Syarofil Anam

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Original article

Leptin levels in childhood tuberculosis and its correlation with body mass index, IFN-γ, and TNF-α in an Indonesian population

Moh Syarofil Anam [a,*], *Maria Mexitalia* [a,b], *Binar Panunggal* [c], *Magdalena Sidhartani* [a], *Banundari Rachmawati* [d], *Hertanto Wahyu Subagio* [e]

[a] *Department of Child Health, Faculty of Medicine, Diponegoro University, Semarang, Indonesia*
[b] *Kariadi Hospital, Semarang, Indonesia*
[c] *Department of Nutrition, Faculty of Medicine, Diponegoro University, Semarang, Indonesia*
[d] *Department of Clinical Pathology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia*
[e] *Department of Clinical Nutrition, Faculty of Medicine, Diponegoro University, Semarang, Indonesia*

ARTICLE INFO

Article history:
Received 4 September 2021
Received in revised form
24 March 2023
Accepted 28 March 2023
Available online xxx

Keywords:
Pediatric tuberculosis
Leptin
Body mass index
Interferon gamma
Tumor necrosis factor-alpha

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-γ, TNF-α, 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-γ, TNF-α, 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 ± 21.46 cm, and Z score BMI was −0.85 ± 1.14 kg/m^2. 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-γ was 2.5 (0.9–161) pg/mL, and TNF-α 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-γ ($r = 0.295$, $p = 0.018$).

Conclusion: There were positive correlations between BMI and leptin levels, whereas IFN-γ and MUAC showed weak correlations.

* *Corresponding author.* Fax: +62248414296, Tel.: +6281367428988.
E-mail address: msanam77@fk.undip.ac.id (M.S. Anam).

https://doi.org/10.1016/j.ijtb.2023.03.012

Please cite this article as: Anam MS et al., Leptin levels in childhood tuberculosis and its correlation with body mass index, IFN-γ, and TNF-α in an Indonesian population, Indian Journal of Tuberculosis, https://doi.org/10.1016/j.ijtb.2023.03.012

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.[1] 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%.[1,2]

Malnutrition is reportedly an important problem in developing countries with high TB morbidity rates and is associated with 2.2 million deaths annually.[3] TB is often accompanied by malnutrition, which can lead to inadequate treatment response and affect disease outcomes.[4,5] 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.[4]

Leptin, a hormone produced by adipocytes, plays an important role in malnutrition in children.[6] 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.[7] 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.[8] Children with TB have been observed to have low leptin levels,[9] which can be detrimental to the host immune system because it causes the cellular response of stimulating macrophages to secrete Th-1, including TNF-α and IFN-γ, which play an important role in TB infection.[10,11] Nevertheless, the relationship between leptin, IFN-γ, and TNF-α in pediatric patients with TB is not yet fully understood.

Therefore, this study aimed to assess the correlation between nutritional status, TNF-α, IFN-γ, 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 2–14 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 ≥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.[12] 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.[13] 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-γ using the human IFN-γ ELISA kit from Elabscience™, human TNF-α 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-γ, <2.0 pg/mL; TNF-α, <15.6 pg/mL; and leptin, 3.7–11.1 ng/mL (for females), and 2.0–5.6 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 ± 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 ± 1.14 SD. The median body weight of the research

Please cite this article as: Anam MS et al., Leptin levels in childhood tuberculosis and its correlation with body mass index, IFN-γ, and TNF-α in an Indonesian population, Indian Journal of Tuberculosis, https://doi.org/10.1016/j.ijtb.2023.03.012

Table 1 – Characteristics of the study subjects.

Variable	Subjects (%)
Age, years (median, [range])	6 (2–14)
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 (9.45–55) 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 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.

Table 2 – Nutritional parameters of the subjects.

Parameter	Subjects (n = 64)
Weight, kg	17.7 (9.45–55)
Height, cm	114 ± 21.46
HAZ (SD)	−1.3 (−4.4–3.13)
Z score BMI	−0.85 ± 1.14
Mid-upper arm circumferences	15.9 (11.5–26.4)
Nutritional status	
Wellnourished	52 (81.3%)
Malnourished	11 (17.2%)
Calorie intake (kcal)	1448.5 (676–4674)
Carbohydrates intake (g)	182.5 (63–558)
Protein intake (g)	57.9 (15.8–191.0)
Fat intake (g)	81.6 (23.6–594.1)
Leptin level, ng/mL	1.2 (0.2–59)
IFN-γ level, pg/mL	2.5 (0.9–161)
TNF-α level, pg/mL	13.0 (5.7–356)

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.

According to the studied laboratory parameters, high IFN-γ values were observed in 35/64 (54.6%) subjects, with a median value of 2.5 (0.9–161) pg/mL. Increased TNF-α was observed in 20/64 (31%) subjects, with a median value of 13.0 (5.7–356) pg/mL, whereas low leptin levels were found in 45/64 (70.3%) subjects, with a median value of 1.2 (0.2–59) ng/mL. Subjects with symptoms of decreased body weight also showed a lower leptin median value of 0.95 (0.4–59.0) ng/mL, compared with 3.3 (0.4–59.0) ng/mL in those without weight loss symptoms, with a significance value of $p = 0.021$; however, there was no difference in nutritional status between these two groups.

Table 3 presents the correlation between the nutritional parameters, IFN-γ, TNF-α, 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.[14]

Malnutrition in childhood TB has long been a concern of experts because it can affect disease outcomes and is associated with high mortality rates.[3–5] 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.[7,9] A meta-analysis by Ye et al. found evidence that leptin levels in patients with TB were lower than that in control subjects.[15] Our study supports these findings, as we similarly observed low leptin levels among our subjects. In contrast, Zheng et al.[16] 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

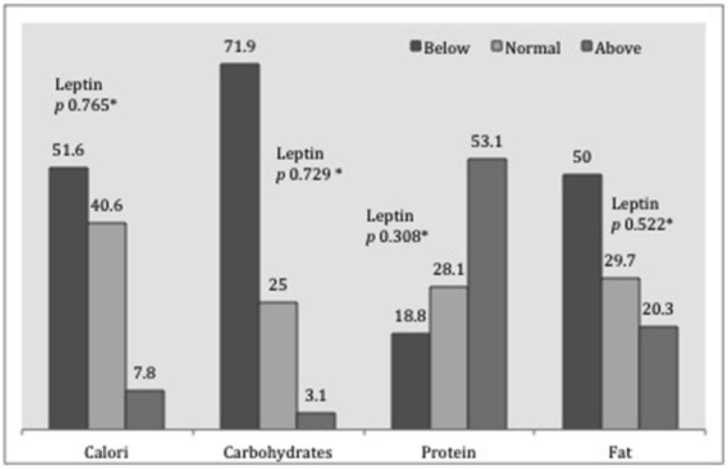


Fig. 1 – Correlation between nutritional intake percentage and leptin level. The data show low intake of calories, carbohydrates, and fat among subjects; however, protein intake was above the normal requirements (the data on nutritional intake values are presented in percentage (%), according to the 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,[17] 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.[17–19]

Table 3 – 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**[a]
BMI Z score	0.453	**0.000**[a]
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-γ,	0.295	**0.018**[a]
TNF-α	0.145	0.252

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

[a] $p < 0.05$ indicates statistical significance; moderate correlation: correlation coefficient of 0.4–0.6; weak correlation: correlation coefficient of 0.2–0.4; no correlation: correlation coefficient <0.2 (Spearman correlation rank test).

Leptin is regulated by the ob gene, with adipocytes as the producers.[18] 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 glucogenesis and gluconeogenesis by regulating blood glucose levels, and leptin levels regulate the balance of nutrient intake.[18,20] 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[21]; 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-γ and TNF-α 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-α and IFN-γ work simultaneously in regulating the inflammatory process in patients with TB.[11] This condition may be influenced by the minimal effect of leptin, which contributes in disrupting the regulation of cytokines under conditions of malnourishment.[22] 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-γ and TNF-α 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.[19,22] IFN-γ will decrease leptin production; however, TNF-α will increase leptin production through the regulation of adipocytes.[23] Patients with TB experience increased immunological activity in response to infection; thus, levels of proinflammatory cytokines such as IFN and TNF will be high at the beginning of the infection.[24] 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,[16,25] including our current study, which only found evidence of a weak correlation between IFN-γ 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-γ and TNF-α. Therefore, further research needs to be conducted using specific levels of IFN-γ and TNF-α. In contrast, studies conducted on obese pediatric patients have proven the correlation between proinflammatory cytokine levels and leptin levels[26] 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-α and IFN-γ 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-γ and leptin levels, and no correlation between TNF-α 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.

Funding

This study was received grant from Diponegoro University number 2143/UN7.5.4/PP/2019.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. World Health Organization. *Global Tuberculosis Report 2020*. twentieth ed. Geneva: World Health Organization; 2020.
2. Ministry of Health Indonesia. *Petunjuk Teknis Manajemen Dan Tatalaksana TB Anak*. Jakarta: Ministry of Health; 2016.
3. Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008;371:243–260.
4. Zachariah R, Spielmann M, Harries A, Salaniponi F. Moderate to severe malnutrition in patients with tuberculosis is a risk factor associated with early death. *Trans R Soc Trop Med Hyg*. 2002;96:291–294.
5. Feleke BE, Feleke TE, Biadglegne F. Nutritional status of tuberculosis patients, a comparative cross-sectional study. *BMC Pulm Med* Oct. 2019;19(1):182. https://doi.org/10.1186/s12890-019-0953-0.
6. Soliman AT, Yasin M, Kassem A. Leptin in pediatrics: a hormone from adipocyte that wheels several functions in children. *Indian J Endocrinol Metab*. 2012;16(3):577–587.
7. Crevel R, Karyadi E, Netea M, Verhoef H, Nelwan R, West C. Decreased plasma leptin concentrations in tuberculosis patients are associated with wasting and inflammation. *J Clin Endocrinol Metab*. 2002;87(2):758–763.
8. Mattioli B, Straface E, Quaranta MG, Giordani L, Viora M. Leptin promotes differentiation and survival of human dendritic cells and licenses them for Th1 priming. *J Immunol*. 2005;174:6820–6828.
9. Setiawati MM, Dewi YO, Pramono A, Anam MS. Effect of tuberculosis treatment on leptin levels, weight gain, and percentage body fat in Indonesian children. *Korean J Pediatr*. 2017;60(4):118–123.
10. Raso GM, Pacilio M, Esposito E, Coppola A, Carlo RD, Meli R. Leptin potentiates IFN-g-induced expression of nitric oxide synthase and cyclo-oxygenase-2 in murine macrophage J774A.1. *Br J Pharmacol*. 2002;137:799–804.
11. Calvacanti YV, Brelaz MC, Andrade JK, Neves L, Ferraz JC, Pereira VR. Role of TNF-alpha, IFN-gamma, and IL-10 in the development of pulmonary tuberculosis. *Pulm Med*; 2012:1–10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3515941.
12. Gie R. *Diagnostic Atlas of Intrathoracic Tuberculosis in Children: A Guide for Low Income Countries*. Paris: International Union Against Tuberculosis and Lung Disease; 2003. http://www.theunion.org/what-we-do/publications/technical/english/pub_diagnostic-atlas_eng.pdf.
13. Graham SM, Ahmed T, Amanullah F, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. *J Infect Dis*. 2012;205(Suppl 2):199–208.
14. Watch V, Aipit J, Kote-Yarong T, et al. The burden of presumed tuberculosis in hospitalized children in a resource-limited setting in Papua New Guinea: a prospective observational study. *Int Health*. 2017;9:374–378.
15. Ye M, Bian LF. Association of serum leptin levels and pulmonary tuberculosis: a meta-analysis. *J Thorac Dis*. 2018;10(2):1027–1036. https://doi.org/10.21037/jtd.2018.01.70.
16. Zheng Y, Ma A, Qiuzhen W, et al. Relation of leptin, ghrelin and inflammatory cytokines with body mass index in pulmonary tuberculosis patients with and without type 2 diabetes mellitus. *PLoS One*. 2013;8(11):1–6.
17. Hussain Z, Khan JA. Food intake regulation by leptin: mechanisms mediating gluconeogenesis and energy expenditure. *Asian Pac J Tropical Med*. 2017;10(10):940–944.
18. Fried SK, Ricci MR, Russel CD, Laferrere B. Regulation of leptin production in humans. *J Nutr Dec*. 2000;130(12):3127s–3131s. https://doi.org/10.1093/jn/130.12.3127S.
19. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature*. 1998;395:763e70.
20. Amitani M, Asakawa A, Amitani H, Inui A. The role of leptin in the control of insulin-glucose axis. *Front Neurisci*. 2013;7(51):1–12. https://doi.org/10.3389/fnins.2013.00051.

Please cite this article as: Anam MS et al., Leptin levels in childhood tuberculosis and its correlation with body mass index, IFN-γ, and TNF-α in an Indonesian population, Indian Journal of Tuberculosis, https://doi.org/10.1016/j.ijtb.2023.03.012

21. Rosenbaum M, Leibel RL. Role of leptin in energy homeostasis in humans. *J Endocrinol*. Oct 2014;223(1):T83–T96. https://doi.org/10.1530/JOE-14-0358.
22. Matarese G, Moschos S, Mantzoroz CS. Leptin in immunology. *J Immunol*. 2005;173:3137e42.
23. Simons PJ, Petra S, Pangaart PS, Roomen CP, Aerts JM, Boon L. Cytokine-mediated modulation of leptin and adiponectin secretion during in vitro adipogenesis: evidence that tumor necrosis factor-a- and interleukin-1b-treated human preadipocytes are potent leptin producers. *Cytokines*. 2005;32:94–103.
24. de Martino M, Lodi L, Galli L, Chiappini E. Immune response to Mycobacterium tuberculosis: a narrative review. *Front. Pediatr.* 2019;7:350. https://doi.org/10.3389/fped.2019.00350.
25. Buyukoglan H, Gulmez I, Kelestimur F, Kart L, Oymak FS, Demir R. Leptin levels in various manifestations of pulmonary tuberculosis. *Mediat Inflamm*. 2007:1–6. https://doi.org/10.1155/2007/64859.
26. Aygun AD, Gungor S, Ustundag B, Gurgoze MK, Sen Y. Proinflammatory cytokines and leptin are increased in serum of prepubertal obese children. *Mediat Inflamm*. 2005;3:180–183.

TURNITIN-Leptin

ORIGINALITY REPORT

17%	13%	13%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.scilit.net Internet Source	1%
2	Jain, M., G. R. S. Budinger, A. Lo, D. Urich, S. E. Rivera, A. K. Ghosh, A. Gonzalez, S. E. Chiarella, K. Marks, H. K. Donnelly, S. Soberanes, J. Varga, K. A. Radigan, N. S. Chandel, and G. M. Mutlu. "Leptin Promotes Fibroproliferative Acute Respiratory Distress Syndrome by Inhibiting Peroxisome Proliferator-activated Receptor-", American Journal of Respiratory and Critical Care Medicine, 2011. Publication	1%
3	www.dovepress.com Internet Source	1%
4	S. Vassiliadis, K. Relakis, A. Papageorgiou, I. Athanassakis. "Endometriosis and Infertility: A Multi-cytokine Imbalance Versus Ovulation, Fertilization and Early Embryo Development", Clinical and Developmental Immunology, 2005 Publication	1%

5	Hosien Shahdadi, Morteza Salarzaee, Abbas Balouchi. "Quality of Life of Diabetic Patients with Smear Positive PTB in Southeastern Iran: A cross-Sectional study in a poor region of Iran", Indian Journal of Tuberculosis, 2017 Publication	1 %
6	www.kjp.or.kr Internet Source	1 %
7	dergipark.org.tr Internet Source	1 %
8	repository.ubn.ru.nl Internet Source	1 %
9	onlinelibrary.wiley.com Internet Source	<1 %
10	worldwidescience.org Internet Source	<1 %
11	www.jrd.or.kr Internet Source	<1 %
12	R. Usha Devi, Sriram Krishnamurthy, B. Vishnu Bhat, Ajit Sahai. "Epidemiological and Clinical Profile of Hospitalized Children with Moderate and Severe Acute Malnutrition in South India", The Indian Journal of Pediatrics, 2015 Publication	<1 %
13	indianpediatrics.net Internet Source	<1 %

14	www.ajbasweb.com Internet Source	<1 %
15	docplayer.net Internet Source	<1 %
16	spotidoc.com Internet Source	<1 %
17	www.medrxiv.org Internet Source	<1 %
18	www.nature.com Internet Source	<1 %
19	Ayse Mete Yesil, Ebru Yalcin, Dilber Ademhan Turhal, Nagehan Emiralioglu, Deniz Dogru, Ugur Ozcelik, Nural Kiper. "From Diagnosis to Treatment of Pediatric Tuberculosis: Ten Years Experience in a Single Institution", Clinical Pediatrics, 2020 Publication	<1 %
20	Bolajoko O. Olusanya. "Is undernutrition a risk factor for sensorineural hearing loss in early infancy?", British Journal of Nutrition, 2009 Publication	<1 %
21	archive.nnl.gov.np Internet Source	<1 %
22	mafiadoc.com Internet Source	<1 %

23	www.banglajol.info Internet Source	<1 %
24	www.researchgate.net Internet Source	<1 %
25	www.ijbs.com Internet Source	<1 %
26	Foster, S.C.. "Dysregulation of the hypothalamic-pituitary-gonadal axis in experimental autoimmune encephalomyelitis and multiple sclerosis", Journal of Neuroimmunology, 200307 Publication	<1 %
27	Lei Chong, Liu Liu, Lili Zhu, Haiyan Li, Youyou Shao, Hailin Zhang, Gang Yu. "Expression Levels of Predominant Adipokines and Activations of STAT3, STAT6 in an Experimental Mice Model of Obese Asthma", Iranian Journal of Allergy, Asthma and Immunology, 2019 Publication	<1 %
28	Leroy C. Folmar. "Effects of chemical contaminants on blood chemistry of teleost fish: A bibliography and synopsis of selected effects", Environmental Toxicology and Chemistry, 02/1993 Publication	<1 %

29	Radheshyam Maurya, Madhulika Namdeo. "Leptin: an immunological adjuvant to improve vaccine response in infectious diseases", Elsevier BV, 2022 Publication	<1 %
30	academic-accelerator.com Internet Source	<1 %
31	edepot.wur.nl Internet Source	<1 %
32	ijabmr.org Internet Source	<1 %
33	Hakan Buyukoglan, Inci Gulmez, Fahrettin Kelestimur, Levent Kart, F. Sema Oymak, Ramazan Demir, Mustafa Ozesmi. "Leptin Levels in Various Manifestations of Pulmonary Tuberculosis", Mediators of Inflammation, 2007 Publication	<1 %
34	clinicaltrials.gov Internet Source	<1 %
35	link.springer.com Internet Source	<1 %
36	spiral.imperial.ac.uk Internet Source	<1 %
37	www.biomedcentral.com Internet Source	<1 %

38	www.karger.com Internet Source	<1 %
39	www.researchsquare.com Internet Source	<1 %
40	Jung-Su Chang, Shiue-Ming Lin, Jane C-J Chao, Yi-Chun Chen, Chi-Mei Wang, Ni-Hsin Chou, Wen-Harn Pan, Chyi-Huey Bai. "Serum ferritin contributes to racial or geographic disparities in metabolic syndrome in Taiwan", Public Health Nutrition, 2013 Publication	<1 %
41	Banu Priya Prathaban, Ramachandran Balasubramanian. "WITHDRAWN: Prediction of epileptic seizures using Grey Wolf Optimized Model Driven mathematical approach", Microprocessors and Microsystems, 2020 Publication	<1 %

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

TURNITIN-Leptin

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6