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CASE REPORT

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Leucine-included liquid diet as medical nutrition therapy improved handgrip strength and mid-upper circumference in clinically malnourished pulmonary tuberculosis patient with high neutrophil lymphocyte ratio: A case report from Universitas Indonesia hospital

Anna Maurina Singal[1], Nadhira Nuraini Afifa[2], Wahyu Ika Wardhani[1], Hario Baskoro[3]

1. *Clinical Nutrition Staff Group, Universitas Indonesia Hospital, Universitas Indonesia, Depok, 16424, Indonesia*
2. *Department of Nutrition, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia*
3. *Pulmonology and Respiratory Medicine Staff Group, Universitas Indonesia Hospital, Universitas Indonesia, Depok 16424, Indonesia*

Abstract

Background and objectives: Muscle weakness delays clinical improvement in pulmonary tuberculosis patients. Higher neutrophil lymphocyte ratio, low handgrip strength, mid-upper arm circumference indicates bad clinical outcome. Weight loss must be managed from the start of treatment. Good muscle condition has benefits to the recovery rate. Leucine provides benefits in increasing the synthesis of muscle mass so as the clinical conditions. Unfortunately, leucine has not been the routine part of medical nutrition therapy in tuberculosis patients.
Methods: This is a case report of a female patient with body weight 42 kg and height 150 cm, admitted to Universitas Indonesia Hospital, with lung tuberculosis. Leucine given, started from 1.95 g/day to the maximum amount of 7,34 g/day through the hospital tailored-made liquid food. There was an improvement of clinical signs and symptoms during 14 days of hospitalization. Mid-upper arm circumferences at day 1, 8, and 15 were 21.1, 21.4, and 12.9 21.9 cm in a row. The right and left handgrip strength at day 1, 8, and 15 were 9.7 kg and 8.1 kg, 10.9 kg and 8.9 kg, 15.1 kg and 13.4 kg, respectively. While the neutrophil lymphocyte ratio at day 0, 6, and 9 were increasing, at 6.89, 6.89, and 13.8, in a row.
Conclusions: Leucine 1.95–7.34 g/day, in tailored-made liquid food, as part of tuberculosis management therapy, though the NLR 13.8, can improve the mid-upper arm circumference, handgrip strength, clinical signs and symptoms in 14 days of hospitalization.

Keywords: tuberculosis, leucine, muscle mass

Corresponding author:
Name : Anna Maurina Singal
Affiliation: Clinical Nutrition Staff Group, Universitas Indonesia Hospital, Universitas Indonesia, Depok, 16424, Indonesia
Email: Maureen_teng@yahoo.com; anna.maurina01@ui.ac.id

Introduction

Southeast Asia ranks fourth in the world's tuberculosis burden in 2021. Specifically, Indonesia is in second place with a tuberculosis burden of 969,000 or 354 per 100,000 population.[1] Tuberculosis patients are vulnerable to malnutrition as a result of the course of the disease. Carlwile et al found that undernutrition is the main risk factor for tuberculosis with a population attributable fraction of 15%.[2] The World Health Organization (WHO) states that increasing calories and protein in tuberculosis patients can provide better recovery rates.[3] The strength of respiratory muscle mass has decreased in tuberculosis patients due to increased tumor necrotizing factor (TNF)-α and other pro-inflammatory cytokines.[4]

Leucine is a branched-chain essential amino acid which has the function of activating the mammalian target of rapamycin complex-1 (mTORC1) signaling pathway in skeletal muscles.[5] This activation causes the initiation of translation and protein synthesis.[5] Leucine is expected to improve the condition of respiratory muscle mass in particular and body muscles. Overall, in people with tuberculosis, the improvement of breathing strength can improve clinical conditions. There are various leucine dosage recommendations to date. In general, adding 4–5 grams of leucine to each main meal can stimulate muscle protein synthesis.[5] The tuberculosis patient in this case report was given liquid food prepared by the hospital, containing leucine, in divided doses in increasing amounts every day. Clinical improvement occurred in this patient. Unfortunately, leucine has not been included as a routine part in nutrition management for the inward patients. This case report shows the benefit of leucine in medical nutrition therapy.

Patient's history

A woman, 53 years old, came to the University of Indonesia Hospital Depok, October 2024, was diagnosed with pulmonary tuberculosis in the 9th month of medication, came with complaints of increasingly severe shortness of breath since the previous five days with a cough with phlegm that was difficult to expel. The patient's weight was 42 kg, and her height was 150 cm. The body mass index showed 18.7 kg/m^2. Muscle wasting occurs in almost every part of the body. The patient has been undergoing treatment at another hospital for the past four days. The clinical condition at that time was compatible with using a nonrebreathing mask of 9 liters/minute (liter per minute). Current laboratory parameters were leukocytes 5,830 10^3/L (N.150–410), neutrophils 81.2% (N. 52–76), blood urea and creatinine respectively 57 mg/dL (N. 15–40) and 0.65 mg/dL (N. 0.5–1). Serum albumin level was 3.2 g/dL (N. 3.5–5.2). Blood gas analysis showed pH 7.345 (7.35–7.45), pCO_2 52.8 mmHg (N. 35–45), HCO_3 29.1 mmol/L (N. 21–25), oxygen saturation 97.6% (N. 95–98), pO_2 105.6 mmHg (N. 75–100). Blood sodium levels were 135 mEq/L (N. 132–147), blood potassium 5.26 mEq/L (N. 3.3–5.4), and chloride 102 mEq/L (N. 94–111). A plain chest radiograph as below shows infiltrates to consolidation and multiple stasis cells in the lower middle field of the right lung, right pleural effusion and left massive pleural effusion.

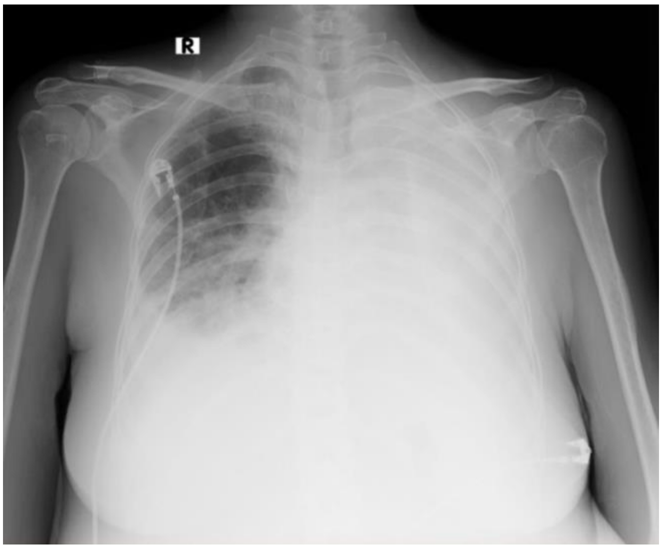

Figure 1. Plain chest radiograph shows infiltrates in the lower middle field of the right lung, right pleural effusion, and left massive pleural effusion

At the start of treatment, the patient experienced severe shortness of breath. She was given a 15 liter per minute of oxygen through the nonrebreathing mask with a breathing frequency of 25 times/minute and the oxygen saturation was 93%. Medical nutrition therapy was given in the form of hospital standard liquid food via a nasogastric tube of 600 kcal or 14 kcal/kg BW with 30 grams of protein or 0.7 g/kg BW/day, and a ratio of nitrogen to non-protein calories was 1: 100. The patient had not been given leucine that day. On the following day, the patient still experienced shortness of breath and was still using a non-rebreathing mask with a breath of 15 liter per minute, oxygen saturation was 96% with a respiratory rate of 25 times/minute. Nutrition was provided in the form of liquid food prepared by the hospital nutrition team, around 500 kcal or 13 kcal/kg BW, with 26 grams of protein or 0.6 g/kg BW/day and nitrogen to non-protein calories was 1:105. Leucine had been started to be given in the amount of 1.95 grams/day. The specific regimens of the Universitas Indonesia Hospital liquid-diet was made of natural food sources of carbohydrate, fat from vegetable oil, and amino acids powder (as leucine included). Each disease has its own specific content of regimen with certain amount of macronutrients, based on individualized calculation.

On the second day of treatment, the patient still experienced shortness of breath. She was still on a non-rebreathing mask of 15 liter per minute, respiratory rate 24 times per minute, oxygen saturation 98%. The calories amount was increased to 800 kcal or 18 kcal/kg BW/day in hospital-specific liquid food with a protein amount of 44 g or 1 g/kg BW. Leucine was increased to 3.06 g. The ratio of nitrogen to non-protein calories is 1:89. The third day of treatment, the shortness of breath got worse. The patient was still in a nonrebreathing mask, 15 liter per minute, breathing frequency 26 times/minute, with oxygen saturation was 93%. The calories was still maintained at 800 kcal, and the protein amount of 1 g/kg BW/day, while the leucine of 3.06 grams. On the fourth day of treatment, the breathing apparatus was changed to a high flow nasal cannula, 40 liter per minute, and oxygen fraction 65%. Respiratory frequency 30 times per minute. Oxygen saturation 97%. Leucine was still being given at 3.06 grams/day.

Then the patient experienced clinical improvement from dyspnea on the fifth day. Breathing was still assisted with a high flow nasal cannula, 40 liter per minute, oxygen fraction 65%. Respiratory frequency 29 times/minute, with oxygen saturation 98%. Nutrition continued to be provided in the form of liquid food with a specific leucine mixture with a leucine amount of 4.08 g. At that time, the total nutrition was 1000 kcal or 23 kcal/kg BW, protein 59 grams or 1.4 g/kg BW with a ratio of nitrogen to non-protein calories of 1:81. At the sixth day of treatment, the patient's shortness of breath improved with the respiratory rate 20 times per minute. She was still in the high flow nasal cannula and the oxygen fraction of 65%, while the oxygen saturation increased to 99%. Nutrition was given at 23 kcal/kg BW with protein 1.5 g/kg BW/day and leucine 4.08 g/day.

The shortness of breath was more improving on the seventh day, while she was still using a high flow nasal cannula with an oxygen fraction of 65%, oxygen saturation of 99%. Hospital-specific liquid food with leucine is given at 1200 kcal or 28 kcal/kg BW/day with a protein amount of 70 g or 1.7 g/kg BW. Leucine reached 4.9 g/day, with a ratio of nitrogen to non-protein calories of 1:82. At the day 8–9 of treatment, the patient was getting better. Breathing had been assisted by a nonrebreathing mask of 10 liter per minute, respiratory frequency of 21 times/minute and oxygen saturation of 99%. She was given 1200 kcal, with a leucine amount of 4.9 g/day through the liquid food, a hospital-specific leucine concoction.

On day 10, she felt less shortness of breath. The speed of oxygen through the non-rebreathing mask was reduced to 9 liters per minute, with oxygen saturation of 99% and respiratory rate 20 times/minute. The route of nutrition delivery was still through enteral route and the calories increased to 1400 kcal or 33 kcal/kg BW/day. The amount of protein was higher to 80 g or 1.9 g/kg BW and leucine is increased to 5.6 g. The nitrogen to nonprotein calories ratio was nearly 1:83. On the eleventh day, the patient was using a simple mask with very minimal shortness of breath. Respiratory frequency 22 times/minute, with oxygen saturation 98%. Nutrition was given to 1600 kcal or 38 kcal/kg BW/day. Protein 93 grams or 2.2 g/kg BW/day and leucine was getting higher to 6.6 g per day. On the 12^{th} day of treatment, the patient was using a nasal cannula with an oxygen saturation of 96%. The nutrition was given around 1800 kcal or 43 kcal/kg BW. The content of protein 104 g or 2.5 g/kg BW/day with high leucine of 7.34 g/day.

At the treatment day 13–15, clinically, the patient was getting much better. Maximum nutrition is given, via oral and enteral, of 1800 kcal or 44 kcal/kg BW/day with a protein amount of 104 grams or 2.5 g/kg BW/day and a leucine amount of 2.45–6.36 g/day. The patient then was dismissed from the hospital. Below in **Table 1** are the results of specific examinations of upper arm circumference and hand grip strength using a CAMRY dynamometer:

Table 1. The upper midarm circumferences, handgrip strength, and neutrophil-lymphocyte ratio changes during hospital days

Period of Hospitalization	Neutrophil Lymphocyte Ratio (NLR)	Mid-upper Arm Circumferences (cm)	Right Handgrip Strength (kg)	Left Handgrip Strength (kg)
Day 0	6.89	-	-	-
Day 1	-	21.1	9.7	8.1
Day 6	6.89	-	-	-
Day 8	-	21.4	10.9	8.9
Day 9	13.8	-	-	-
Day 15	-	21.9	15.1	13.4

Discussion

Tuberculosis infection is caused by *Mycobacterium tuberculosis* which can be life threatening. Sarcopenia, namely a decrease in muscle mass and strength, is often found in tuberculosis sufferers, especially the elderly.[6] Failure of pulmonary tuberculosis therapy can increase the risk of morbidity, drug resistance, bacterial transmission and mortality. Diallo et al (2018) concluded that weight loss that occurs from the time of diagnosis until the first sputum smear examination is related to failure of tuberculosis therapy (aORL 2.5). Therefore, weight loss must be managed from the start of treatment.[7] Paton et al found that tuberculosis patients had low body weight, fat-free mass and fat mass. Areas of fat-free mass that experience a decrease are the torso and extremities.[8]

Tuberculosis infection can increase the production of interleukin-6 (IL-6) which will reduce body weight, including muscle mass.[9] A decrease in respiratory muscle mass can typically be found in tuberculosis patients with chronic obstructive pulmonary disease.[10] The muscle mass index at low levels are closely related to decreased immune function and are a risk factor for tuberculosis infection.[11] The patient's body mass index in this case was 18.7 kg/m^2. According to the Asia-Pacific BMI criteria, the patient was still in normoweight status, while the malnutrition perse can be based on the Global Leadership Initiative on Malnutrition (GLIM) criteria by ESPEN. The muscle wasting of this patient was found in all areas of the body. It was clearly also found with the measurement of right and left handgrip strength at first day of hospitalization were 9.7 kg and 8.1 kg respectively. The muscle strength of tuberculosis patients was previously found decreased when the patients were initiated with the antituberculosis medication.[12] While other study conducted in 2017 by Choi et al, found that tuberculosis survivors had increased risk of sarcopenia and osteoporosis.[13]

Leucine given to patients is a minimum of 1.95 g/day (on the first day of treatment) and a maximum of 6.36 g/day (on the last day of treatment). According to Volpi, the leucine dose can be given at 3-4 grams per meal or according to Casperson and Murphy, leucine can be given at 4-5 g combined with regular food. The recommended dose of leucine by WHO is 39 mg/kg BW/day and Canada is 34 mg/kg BW/day, which is still relatively low compared to actual needs, based on research by Szwiega et al, which can reach 120 mg/kg BW/day.[14,15,16]

Based on the rule of thumb from Canada and WHO, this patient should only be given 1428 mg (1,428 g) and 1638 mg (1,638 g) of leucine per day. However, according to Szwiega et al, leucine can reach 120 mg/kg BW/day or 5050 mg (5.05 g) per day. The patient in this case received a minimum of 1.95 g of leucine per day, exceeding the recommended dose of leucine by Canada, by 136%, and by WHO by 119%. Leucine comes from many sources naturally, such as leucine content per 100 g of these are chiken's breast 1,955 g of leucine, lamb 1,532 g of leucine, cod contain 1,484 g of leucine, bread contains 0,691 g of leucine.[14] While in this case report, the leucine came from the commercial amino acid powder product to be included in as the tailored-made of liquid food. The upper limit of safe intake for leucine amino acid for healthy adults is 530 mg/kg BW/day and up to 550 mg/kg BW/day.[17,18, 19,20]

The patient's clinical improvement during the treatment period was visible day by day, with improvements in respiratory effort, respiratory frequency, oxygen saturation, and rapid weaning, changing breathing aids from high flow nasal cannula to non-rebreathing mask, then simple mask, and nasal cannula. At the early phase of clinical onset, this patient experienced shortness of breath. It was as considered with the study conducted by Aytac et al, that the subjects reported tiredness after diagnosis of tuberculosis. They were examined for the Piper Fatigue Scale.[21] With the adequate supply of the amino acid leucine in this patient, the maximum administration reached 7.34 g/day. This dose is reached within 12 days of treatment. Eventually, there was an improvement of clinical signs and symptoms of this patients.

Leucine has a main function in activating the mammalian target of rapamycin complex (mTORc)-1 signaling pathway so that the respiratory muscles of these patients can also be stimulated to initiate translation and protein synthesis. Apart from being linked to muscle mass, leucine also has anti-inflammatory effects. This can be seen in research by Nicastro et al. which shows a decrease in the cytokine interleukin (IL)-6, tumor necrotizing factor alpha (TNF alpha) and increased anti-inflammatory cytokine interleukin (IL)-10 by amino acids leucine in eight healthy men.[22] There has been no further research regarding the anti-inflammatory effects of the amino acid leucine in tuberculosis patients. In this case, the levels of IL-6, TNF-alpha, and IL-10 were not checked. The patient was given the tuberculosis drug 2 fixed-dose combination (FDC) 1 times 3 tablets at 9th month for 9th month of medication. Tuberculosis regimens that are available as fixed-dose combination and separate tablets, make the patients adhere more so they can complete the tuberculosis treatment.[23]

Neutrophil-to-lymphocyte ratio (NLR) may be a helpful method for risk categorization in the adult latent tuberculosis infections in the United States.[24] Sormin et al confirmed that there was a significant difference of NLR between bacteriological confirmed tuberculosis patients and multidrug resistant tuberculosis patients, while the value of NLR <2.91 was suggestive for multidrug resistant tuberculosis.[25] Study from Yin et al, mentioned that the NLR >2.53 is predictive of pulmonary TB retreatment.[26] This was found in this case report that at the early period of being hospitalized, the NLR of this patient was 6.89. In tuberculosis meningitis patients, the NLR value is an independent predictor of short-term prognosis in patients with tuberculosis, especially tuberculous meningitis. Patients with NLR values >9.99 have poor survival.[27] This patient at day 9 of hospitalization, the NLR increased to 13.8. It is quite interesting that this NLR is in high value that would result in worse prognosis and survival.

However, the patient experienced clinical improvement, with the provision of adequate nutrition good, especially the high amount of the amino acid leucine, namely 7.34 g/day in hospital-specific leucine-concocted liquid food. This also had some beneficial effect in the upper midarm circumferences during hospitalization period. This patient had an increase in circumferences, from 21.1 cm to 21.9 cm in 14 days. The mid-upper arm circumferences can be a useful tool for a fast assessment of the nutrition status.[28] Arm has components such as subcutaneous fat and muscle. Decreament of mid-upper arm circumferences reflects that there is muscle loss or subcutaneous tissues. Changes in mid-upper arm circumferences can be a tool also for the successful of medical nutrition therapy.[29] According to study initiated by Tungdim, et al, said that the prevalence of undernutrition based on mid-upper arm circumference <22 cm was found to be 64.8% of Indian tuberculosis patients.[30] Tuberculosis patients were found in severe malnourished conditions, accelerated with the low of mid-upper arm circumferences length.[31.32,33,34] and also the reduction muscle strength.[35,36] There was an improvement of handgrip strength in tuberculosis patients who got the antituberculosis therapy, whom was evaluated at the 2nd and 6th month after the therapy was started.[37] Low handgrip strength also associated with nontuberculous mycobacterial pulmonary disease.[38,39] The functional capacity especially for the muscle mass, reflected by the measurement of right and left handgrip strength, were improved. As leucine supplementation is safe and effective to enhance muscle protein synthesis and reduce loss of lean mass in catabolic situations, such as infection.[40]

Conclusion

As this patient in this case report was given medical nutrition therapy, as the part of tuberculosis management, as early as she was admitted to the hospital. Leucine 1.95–7.34 g/day, in tailored-made liquid food, as part of tuberculosis management therapy, though the NLR 13.8, can improve the mid-upper arm circumference, handgrip strength, clinical signs and symptoms in 14 days of hospitalization.

Conflict of interest

The authors declared no conflict of interest regarding this article.

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