Malnutrition and lung cavity formation in pulmonary tuberculosis patients

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Abstract

Background: Tuberculosis (TB) is an infectious disease and still a major public health threat globally, also one of the leading causes of death worldwide. One of the characteristics found in pulmonary TB patients is lung cavity on their chest radiograph. This is related to many aspects, including slower conversion of sputum cultures, treatment failure and relapse, drug resistance, higher bacillary load, even higher infection transmission rates. Some studies before had found that the lung cavity is affected by many factors, such as elder age, sex, diabetes mellitus, and malnutrition. Meanwhile, malnutrition itself in pulmonary TB patients is found to be related to each other, this article review how malnutrition affects the formation of lung cavity in pulmonary TB patients.

Objective: To observe the relationship between malnutrition and lung cavity formation in pulmonary tuberculosis patients.

Method: In this paper, we provide a literature review. The method to achieve the objective consists of using literature exploration, which was conducted from October 2022-February 2023 by searching the relevant studies from several databases.

Results: Cavity formation in pulmonary TB patients is a complex mechanism from many factors contributing, including the immune system of the host. Studies show that malnutrition in pulmonary TB patients plays important role linked to lung cavity formation since malnutrition affects both innate and cellular immune response in host.

Conclusion: Malnutrition is more predominating in pulmonary TB patients and is related to incidence of lung cavity in pulmonary TB patients, therefore plays role in the severity of the disease in pulmonary TB.

Keywords: nutritional status, malnutrition, lung cavity, pulmonary tuberculosis

Introduction

Tuberculosis (TB) is an infectious disease caused by the bacillus Mycobacterium tuberculosis, which spreads when people with TB expel the bacteria into the air (by coughing). This disease usually affects the lungs, known as pulmonary TB, although it can also affect other organs. TB is a major cause of poorer health-outcome and one of the leading causes of death worldwide. Until the Corona Virus Disease-2019 (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent and was the thirteenth leading cause of death globally.1 Reporting from the Indonesian tuberculosis website managed by
the Ministry of Health, estimates of pulmonary TB cases in Indonesia in 2022 are around 459,789 cases with an estimated death rate due to TB of 107,000 or 40 per 100,000 population. This is a problem because it is certainly the opposite of one of the targets of the Sustainable Development Goals (SDGs) of the World Health Organization (WHO), namely ending the TB epidemic by 2030.1

The appearance of a lung cavity on radiological examination, which accounts for more than 40% of people with pulmonary TB at the time of diagnosis, is one of the most often observed clinical signs of TB.3 Cavities are a defining feature of TB disease and add to the disease’s dismal prognosis. Compared to TB without cavities, pulmonary cavity will result in slower conversion of sputum cultures, subpar clinical results, and increased infection transmission rates.3,4 This is because cavities are associated with a greater infection rate possibly due to a higher burden of organisms. In addition, between 20–50% of cavitary TB patients have a persistent cavity even after completion of anti-TB treatment due to incomplete healing and formation of fibrotic scar tissue.4 Presence of a lung cavity is also associated with treatment failure and relapse among pulmonary TB patients.5 Some studies have found several risk factors associated with the lung cavity, such as older age, gender, diabetes mellitus, and malnutrition.3,6-9 It has long been known that there is a relationship between TB and malnutrition, malnutrition promotes the development of active TB, and active TB exacerbates malnutrition.10

Malnutrition is a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease.11 The prevalence of malnutrition in patients with TB is estimated to range from 50% to 57%, and malnutrition is associated with a two-fold risk of death.12,13 Malnutrition may specifically weaken cell-mediated reactions that are crucial for preventing and controlling TB, according to some researches.9 Malnutrition, which also indicates a nutritional deficiency and is linked to increased pulmonary inflammation, as well as a number of other conditions like chronic energy deficiency, frequent pulmonary inflammation, elevated oxidative stress, and altered body composition, may also play a role in the development of a cavity in pulmonary TB.14

Methods

This review was designed as a literature review to analyse the existing data and information about the relationship between malnutrition and lung cavity formation in pulmonary TB patients. Literature was explored from the following databases: PubMed, ScienceDirect, Web of Science and Google Scholar. All databases were searched from October 2022 to February 2023 and literature from the last 10 years of publication was chosen for this review. A combination of these keywords addressing “malnutrition” or “nutritional status”, “lung cavity”, “cavity formation”, and “pulmonary tuberculosis” were used. There were no language restrictions set in the search strategy. Firstly, the titles and abstract of relevant articles were screened and the full articles were read and observed to identify the eligible studies to be included in this review.

Discussion

Cavity formation in pulmonary tuberculosis

Lung cavity has been defined as a process that begins with caseous lung necrosis, resulting in caseous pneumonia. This in turn causes damage to the alveolar, septal, bronchial, and blood vessels, forming a cavity when the area of caseous pneumonia liquefies, whose contents are released during coughing. The cavity consists of a layer of necrosis on top of the granulomas lipid and may be surrounded by a collagen capsule after tissue repair.15 There is ongoing discussion over how cavities occur in TB. Serial radiological observations revealed that TB cavities develop from pre-existing regions of lung that are too packed, which then erode the nearby airways. Histological findings showing structural similarity between necrotic granulomas and cavity walls lend credence to this notion. These studies also found two additional morphological alterations required
for cavity formation: central necrosis and extracellular matrix depletion.\textsuperscript{10} Cavity formation is the transformation of immune-containing lung tissue into a surface layer of lung tissue protected by immune cells from the outside environment. The TB cavity is a complex phenotype that is influenced by biochemical, biophysical, immunological, and microbiological mechanisms, all of which are crucial for cavity creation at different stages.\textsuperscript{4}

Tuberculous cavity development is typically referred to as a "post-primary" process since it happens decades or even centuries after the initial "primary" infection. It has been proposed that liquefaction, which occurs when areas of caseous necrosis liquefy and create an environment for fast bacterial growth, is a crucial step in the creation of TB cavities. Although the lipid content of the caseous centre lacks enzymatic activity and is unable to dissolve the three-helix structure of collagen, which gives the lung its tensile strength, the areas of caseous necrosis are rich in lipids. Consequently, the buildup of lipid-rich necrotic material must be a part of a multifaceted disease process. These occurrences could include lipid buildup, cell death, DNA lysis of dying host cells, and extracellular matrix damage.\textsuperscript{17}

Other study also supports this theory by stating that in the process of cavity formation, host lipids and mycobacterial antigens accumulate in the alveoli but only small number of bacteria are present then sudden necrosis related to a delayed-type hypersensitivity reaction against mycobacterial antigens occurs. The lipid-rich necrotic material in granulomas does not have the enzymatic activity to degrade collagen and consequently, its build-up is only one component of cavity formation. Extracellular matrix breakdown takes place and involves matrix metalloproteinase (MMPs). Indeed, increased concentrations of MMPs have been found in TB cavities along with other study before, also neutrophils have also been found in cavities.\textsuperscript{17,18}

**Factors contributing to cavity formation**

Based on the epidemiologic triad, there are three main components that contribute to cavity formation in pulmonary TB patients; host, agent, and environment.\textsuperscript{19} The formation of cavity lesions in pulmonary TB patients is closely related to the host’s defense response. The innate immunity plays a major role in the host’s response to\textit{M. tuberculosis}. Macrophages are the first line of defense and their response can either control the infection or favor its development. While there is extensive data describing the role of the innate immune response in pulmonary TB, there is still more work to be done to better understand its role leading to lung cavity. Necrosis is associated with cavitation in many processes, such as squamous cell carcinoma and pyogenic lung abscess. Similarly, the relative tendency toward cell necrosis over apoptosis during the inflammatory response to \textit{M. tuberculosis} infection is a likely factor affecting cavitation. Therefore, cell-signalling pathways that favor necrosis over apoptosis could also bias the inflammatory response toward cavity formation.\textsuperscript{4}

In addition to those findings, type-I immune dominance during TB was shown by the predominance of CD4+ and CD8+ T cells responsive to \textit{M. tuberculosis} antigens by rapid gamma interferon (IFN-\(\gamma\)) and alpha tumor necrosis factor (TNF-\(\alpha\)) synthesis. These cells were found in both radiologically involved in pulmonary sites but were conspicuously reduced in areas of cavity formation. Study indicates that proportions of TNF-\(\alpha\) and IFN-\(\gamma\) producing cells within both the CD4+ and CD8+ subsets were significantly reduced in TB patients with cavities. However, the IFN-\(\gamma\) and TNF-\(\alpha\) responses of both CD4+ and CD8+ T lymphocytes from TB patients were remarkably impaired in those individuals with lung cavities. Cavitation has also been reported to be associated with local neutrophilia and relative lymphopenia. Studies show that TB patients with cavities had higher absolute numbers of neutrophils than did patients with infiltrates. The accumulation of neutrophils together with these impaired \textit{M. tuberculosis} specific lymphocyte responses probably plays an important role in the pathogenesis of cavity TB.\textsuperscript{20}

Secondly, pathogenic factors may also contribute to the process of lung cavity formation where research is still being carried out to look for
these factors. Recently genetic variability and strain differences in *M. tuberculosis* have been considered and thought to have contributed to the pathogenesis of the disease. A few factors responsible for the genetic variation among *M. tuberculosis* complex (MTBC) members have been identified. For instance, the small genetic variation in MTBC could be due to disparity in the location and copy number of an insertion (IS) sequence specific (IS6110) form of *M. bovis* and *M. tuberculosis*. Variation in MTBC could also be due to short DNA sequences known as region of difference (RD). Another study was also found that there were branched-evolved sub-clones with a genetic distance between them of 10 ~ 14 SNPs in cavity lesions of pulmonary TB patient.

From environment factors, study found that smoking was associated with more extensive lung disease and lung cavity. This finding was related to impairment of the ability of THP-1 cells and primary human alveolar macrophages in controlling *M. tuberculosis* infection caused by nicotine. One mechanism by which nicotine impairs macrophage control of *M. tuberculosis* is via inhibition of autophagy as nicotine induces NF-κB activation. Another study supported this finding by indicating that the pulmonary immune compartment of smokers compared with nonsmokers is replete with high numbers of alveolar macrophages that demonstrate specific immune impairments that would weaken the host immune response to *M. tuberculosis* infection. Nicotine also has the capacity to inhibit production of proinflammatory cytokines, like TNF-α, IFN-γ, and IL-1β, that necessary for host defense against microbes. It was also found in previous study where *M. tuberculosis* infection of nonsmokers’ alveolar macrophages induces a significant increase in TNF-α, IFN-γ, and IL-1β compared with uninfected cells. This increase in key cytokines was not seen in alveolar macrophages from smokers after *M. tuberculosis* infection. Furthermore, nicotine can also promote phenotypic expression of other Th cell types, specifically promote Th2 adaptive immune response, that can deleteriously impact host immunity against *M. tuberculosis*.

**Malnutrition and lung cavity formation in pulmonary tuberculosis**

Nutritional status is one of the most important determinants of resistance to infection. It is generally known that immune system impairment is linked to dietary deficiencies. Infection can cause nutritional stress and weight loss, which can affect immune function and nutritional status while malnutrition reduces cell-mediated immunity and increases susceptibility to infection. In 2013, WHO issued its first guidelines on nutritional care and nutritional support for patients with TB. In this guideline, WHO emphasizes that all patients with active TB receive individual nutritional assessment and management, including dietary counselling and nutritional interventions, to improve nutritional status so that it is hoped that it can prevent TB treatment failure. Malnutrition without disease and disease-related malnutrition has established may coexist in TB patients, once an active disease has developed. The latter is frequently triggered by a combination of appetite loss, malabsorption, and/or catabolism triggered by inflammation. Chronic malnutrition is characterized by a reduced body mass index (BMI). According to studies, malnutrition affects 50% to 57% of TB patients.

Study from Boston University about effect of malnutrition on radiographic findings in pulmonary tuberculosis found that those with severe malnutrition were more likely to have lung cavity formation (OR 3.4, 95%CI: 1.2-9.8) from univariate analysis and in adjusted multivariable analysis, subjects with severe malnutrition were more likely to have lung cavity (adjusted OR 4.6, 95%CI: 1.5-14.1, p=0.03) than those with normal BMI, controlling for smoking. These findings were also supported by data from Kazakhstan where lower BMI is found to be one of the factors associated with fibro-cavernous TB identified by the presence of lung cavity. The binary logistic regression showed that lower BMI (unadjusted OR 6.3271, 95%CI: 2.6746-14.9673, p<0.0001) was associated with fibro-cavernous TB; and multivariate logistic regression analysis confirmed that lower BMI (adjusted OR 5.719, 95%CI: 2.049-15.965, p=0.001) was significantly
associated with fibro-cavernous TB. It is likely that malnutrition has an immunomodulatory effect because it has been found to be linked to more severe radiographic illness. The term nutritionally acquired immune deficiency syndrome refers to the primary cause of acquired immunodeficiency, which is malnutrition. Effective innate and adaptive immune response, typified by a potent T-helper 1 response and granuloma formation, is required for M. tuberculosis containment. Malnutrition has been associated to increase T-helper 2 and T-regulatory cells while decreasing T-helper 1. This also may be due to activation of inflammatory process in particular, the presence of nutritional deficiencies and is associated with increased lung inflammation in malnutrition. In the event that these combined impacts on the immune system change the aetiology of TB in the setting of malnutrition and lead to more lung cavity.

Another study conducted by Kim, et al with mean BMI 21.8 (18.2-25.4) kg/m² showed that from univariate analysis, BMI (unadjusted OR 0.90, 95%CI: 0.84-0.96, p=0.002) was significantly associated with cavitary TB. Moreover, from its multivariate analysis, BMI (adjusted OR 0.88, 95%CI: 0.81-0.97) was significantly associated with cavitary TB after adjusting for age, sex, BMI, previous history of TB, smoking, comorbidities, initial AFB smear, NAAT, and bilateral involvement in chest x-ray. These findings were also supported by study conducted by Koo, et al showed that BMI was significantly associated with the presence of cavities (OR 0.824, 95%CI: 0.67-1.01). There have been reports that BMI is inversely associated with the risk of TB. This means obesity presented a protective effect, while a lower BMI was associated with the development of TB and higher TB-related mortality. In their study population, it is found that lower BMI was related to the presence of lung cavity and leading to poor compliance to treatment in pulmonary TB patients. The host's immunity and the preponderance of T-helper-2 CD4+ cells in the alveoli are linked to lung cavity formation in TB patients. A lower BMI is correlated with higher pulmonary inflammation and free neutrophil elastase activity in the lungs and is indicative of a dietary insufficiency. The development of a cavity in pulmonary TB may be influenced by a number of circumstances linked to a reduced BMI, including chronic energy shortage, recurrent pulmonary inflammation, increased oxidative stress, and changed in body composition.

Besides BMI, another component defining malnutrition is biochemical marker, such as albumin and neutrophil/lymphocyte ratio (NLR). The study investigated the association between pre-treatment immunonutritional status and lung cavity in patients with pulmonary TB in Japan has another supporting result. Compared with patients in the non-cavitary TB group, patients in the cavitary TB group had significantly higher neutrophil and platelet count, with marginally low lymphocyte count and serum albumin level. Regarding NLR, prognostic nutritional index (PNI), platelet to lymphocyte ratio (PLR), and BMI, the cavitary TB group had significantly higher NLR and PLR than the non-cavitary TB group (p=0.005 and p=0.009, respectively). In univariate analyses, low serum albumin (<3 g/dL), high neutrophil count (>6000/mm³), low lymphocyte count (<1000/mm³), high NLR (>5), and high PLR (>200) were associated with lung cavity. Further in the multivariate analysis, statistically significant associations were observed between lung cavity and high NLR and low serum albumin level (p=0.014 and p=0.025, respectively). An increase in neutrophils, as the main cells engaged in inflammation and the host’s defense against bacterial infection, has been linked to a decrease in lymphocyte count. A lower lymphocyte count, which is indicated by an increased NLR, may lead to a weaker lymphocyte-mediated immune response. It is also conceivable that changes in the relative proportions of circulating lymphocytes could affect the development of lung cavity because macrophages and T lymphocytes play crucial roles in lung cavity in pulmonary TB patients. The results of the present study indicated that malnutrition and increased severity of inflammation might be associated with lung cavity in pulmonary TB patients.
Conclusion

Malnutrition is a condition resulting from lack of intake or uptake of nutrition that leads to altered body composition and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease. In pulmonary TB patients, there are two types of malnutrition that can be taken place: malnutrition without disease and disease-related malnutrition. Malnutrition itself can be described from body composition using BMI and biochemical marker using NLR and albumin. According to some studies, lower BMI and changing in immunonutritional status, indicating malnutrition condition, is more predominating in pulmonary TB patients with cavity. Malnutrition needs to be treated since it is linked to increased cavitation and the severity of the disease in pulmonary TB. All viable strategies should be assessed and tailored to the needs of the nation as we work toward the End TB goals in 2030 as stated by WHO.

Conflict of Interest

The authors declare that there is no conflict of interest regarding this article.

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