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Hookworm infection among patients with pulmonary tuberculosis: Impact of co-infection on the therapeutic failure of pulmonary tuberculosis

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ABSTRACT

Objective/background: The aim of this study is to determine the rate of hookworm infection among patients with pulmonary tuberculosis (TB) and to find out if there is a relation between hookworm infection and the therapeutic failure of pulmonary TB.

Methods: We carried out a prospective, hospital-based study. The study included 231 naïve patients with pulmonary TB, consecutively. Patients were evaluated at the 4th month of therapy for persistence of *Mycobacterium tuberculosis* infection. All patients had clinical evaluation, laboratory investigations (including sputum culture and stool microscopic examination), and imaging studies (abdominal ultrasonography and chest radiography).

Results: The study population mean age was 42.7 ± 13.9 years old with 26.8% of them 40 years old or more. Out of 231 patients, 133 (57.6%) were men. Therapeutic failure rate of pulmonary TB was 29.4%. Hookworm infection was diagnosed among 16.5% of patients and 27.7% had diabetes mellitus (DM). Using multivariate analysis, it was found that age of 40 years or more (odds ratio [OR] 8.4; 95% confidence interval [CI] 1.7–41.3; $p = .009$), hookworm infection (OR 7.6; 95% CI 1.2–49.9; $p = .034$), and DM (OR 5.9; 1.2–28; $p = .027$) were independently associated with therapeutic failure of pulmonary TB among the study population with pulmonary TB.

Conclusion: In conclusion, the rate of therapeutic failure of pulmonary TB is high. Besides older age and DM, hookworm infection can reduce the therapeutic response of pulmonary TB. Screening for and control of DM and hookworm infection among patients with pulmonary TB may improve their therapeutic response.

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Introduction

Tuberculosis (TB) is a major global health problem, with an estimated 9 million new cases and 1.5 million deaths during 2013 according to the World Health Organization (WHO) [1]. The standard four-drug regimen (isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months followed by isoniazid and rifampin for 4 months) has high efficacy in achieving cure rates (90–95%) [2]. To monitor pulmonary TB patients, culture examinations are recommended at monthly intervals until two consecutive culture specimens are negative at the end of treatment [3]. According to WHO, the therapeutic failure of pulmonary TB is defined as positive sputum culture at the 4th month or later during treatment [4]. The gold standard for the diagnosis of TB is culture [5].

More than 500 million people are infected with hookworm globally. The diagnosis of hookworm infection is made with microscopic identification of the characteristic ova in stool [6]. The overlapping distribution of hookworm infection with other pathogens results in a high rate of coinfection [7]. It was speculated that helminth infections, including hookworm, may adversely influence the host–immune response to other infections, especially to intracellular pathogens such as *Mycobacterium tuberculosis* (Mtb) [8,9]. This has lead to the suggestion that helminth infection may increase both the susceptibility to, and the disease progression of, bacterial diseases. This hypothesis is based on the observation that helminth infections results in eosinophilia, elevated immunoglobulin E, and mast cell activation, suggestive of the enhanced cytokine response by type 2-T-helper cells (Th2) and a concomitant suppression of a type 1-T-helper cells (Th1) response, which is often involved in the protection against intracellular pathogens [10].

Both pulmonary TB and hookworm infections are common diseases in Egypt. The therapeutic failure of pulmonary TB is not uncommonly encountered in upper Egypt. We lack studies exploring the impact of hookworm infection on the rate of therapeutic failure among patients with pulmonary TB. The aim of this study is to determine the rate of hookworm infection among patients with pulmonary TB, and to find out if there is a relation between hookworm infection and the therapeutic failure of pulmonary TB.

Materials and methods

We carried out a prospective, hospital-based study at Assiut University Hospital during the period of June 2011 to November 2014. The study included 231 naïve patients with pulmonary TB, consecutively. Pulmonary TB was diagnosed based on positive sputum culture on Löwenstein–Jensen medium performed by an experienced microbiologist, with or without evidence on chest radiography [5]. All patients received the WHO-recommended therapy: isoniazid (5 mg/kg/day), rifampin (10 mg/kg/day; maximum dose was 600 mg/day), ethambutol (20 mg/kg/day; maximum dose was 1600 mg/day), and pyrazinamide (30 mg/kg/day; maximum dose was 2000 mg/day) for 2 months, followed by isoniazid and rifampin for 4 more months [11]. Therapeutic failure of pulmonary TB was defined as positive sputum culture at the 4th month or later during treatment [4]. The diagnosis of hookworm infection was made with microscopic identification of the characteristic ova in stool [6] performed by an experienced parasitologist using three consecutive stool samples. Patients with extrapulmonary TB or intestinal parasitic infection other than hookworm infection were excluded from the study.

Patients were evaluated at the 4th month of therapy for persistence of Mtb infection. All patients had clinical evaluation, laboratory investigations, and imaging studies. Laboratory investigations included sputum culture on Löwenstein–Jensen medium, stool microscopic examination, complete blood count, liver chemistry, kidney chemistry, fasting level of serum glucose, and testing for antibody to human immunodeficiency virus. Imaging studies included abdominal ultrasonography and chest radiography. Long-term use of either proton pump inhibitors or corticosteroids was defined as use for 1 month or more during treatment for pulmonary TB.

Ethical considerations

The study was approved by the Faculty of Medicine Clinical Research Ethical Committee (Assiut University), and was carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). Before enrollment in the study, all the participants signed a consent certificate. Before signing, they were able to discuss in detail with the investigator the certificate subjects and the study aim. The participants were clearly informed that refusing to participate in the study will not affect having full benefit of the available medical service and treatment. Data were collected by personal interview with the participants taking in consideration data confidentiality.

Statistical analysis

The data were entered and analyzed using the Statistical Package for Social Sciences ((SPSS, Chicago IL, USA) for windows, version 22). Results were expressed as mean ± standard deviation or frequency (percentage) as appropriate. To compare the distribution of demographic criteria between patients with and without therapeutic failure of pulmonary TB, we used Chi-square test. Predictors of the therapeutic failure of pulmonary TB were identified using univariate analysis (Yates' corrected Chi-square test) then multivariate analysis (stepwise binary logistic regression) to assess the specific effect of each predictor. Multivariate analysis included factors with significant level ($p < .05$) in univariate analysis.

Results

The study included 231 patients diagnosed as having pulmonary TB. The demographic criteria of the study population with pulmonary TB are shown in Table 1. Their mean age was 42.7 ± 13.9 years old, with 26.8% of them being 40 years of age

Table 1 – The demographic criteria of the study population with pulmonary tuberculosis (*n* = 231).

Age (y)	42.7 ± 13.9
Age (⩾40 y)	62 (26.8)
Gender (male)	133 (57.6)
Residence (rural)	159 (68.8)
Therapeutic failure of pulmonary TB	68 (29.4)
Hookworm infection	38 (16.5)
Corticosteroids (long-term use)	50 (21.6)
Proton pump inhibitors (long-term use)	48 (20.8)
Chronic obstructive pulmonary disease	60 (26)
Congestive heart failure	21 (9.1)
Obesity	43 (18.6)
DM	64 (27.7)
Renal insufficiency	25 (10.8)
Liver cirrhosis	36 (15.6)

Note. Apart from "Age", all values are given as *n* (%).
DM = diabetes mellitus; *n* = number; TB = tuberculosis.

or more. Out of 231 patients, 133 (57.6%) were men. The rate of therapeutic failure of pulmonary TB was 29.4%. Hookworm infection was diagnosed among 16.5% of patients, and 27.7% had diabetes mellitus (DM). None of the study population had human immunodeficiency virus infection.

Table 2 shows the factors associated with the therapeutic failure of pulmonary TB among the study population with pulmonary TB. Using univariate analysis, it was found that an age of 40 years or more, hookworm infection, long-term use of corticosteroids, chronic obstructive pulmonary disease, congestive heart failure, and DM were associated with the therapeutic failure for pulmonary TB.

Using multivariate analysis of the factors associated with the therapeutic failure of pulmonary TB on univariate analysis, it was found that an age of 40 years or more [odds ratio (OR) 8.4; 95% confidence interval (CI) 1.7–41.3; $p = .009$], hookworm infection (OR 7.6; 95% CI 1.2–49.9; $p = .034$), and DM (OR 5.9; CI 1.2–28; $p = .027$) were independently associated with the therapeutic failure of pulmonary TB among the study population with pulmonary TB (Table 3).

Discussion

Our study has revealed a high rate of therapeutic failure of pulmonary TB (29.4%). This rate is much higher than expected (10%) after 2 months of treatment with isoniazid, rifampin, ethambutol, and pyrazinamide, followed by 4 months of treatment with isoniazid and rifampin [2], and is modestly higher than the rate (15%) reported by Ditah et al. [12]. However, this rate among our study population is very close to that reported among the Korean patients (30%) [13]. This observation reflects that we are facing difficulty in treating pulmonary TB in our locality. Besides Mtb resistance to antimicrobial therapy, other factors contributing to the relatively high rate of the therapeutic failure have to be explored.

Among our study population with pulmonary TB, predictors of the therapeutic failure of pulmonary TB were being aged 40 years or more, hookworm infection, and DM. In agreement with our study findings, advanced age was one of the independent risk factors of the therapeutic failure of pulmonary TB [12,14]. Several studies reported this association with different discriminant points of age. The highest point (55 years old or more) was reported as a predictor of therapeutic failure of pulmonary TB by Muñoz-Sellart et al. [15], while the lowest one (45 years old or more) was reported by Cruz-Hervert et al. [16]. Inbetween, it was found that an age of 50 years or more (OR 3.11; 95% CI 1.17–8.26) [17], or 46 years or more (OR 6.71; 95% CI 1.61–28) [18] were predictors of the therapeutic failure of pulmonary TB. Immunological control of TB is based on CD4+ T-cell-produced gamma interferon with subsequent activation of macrophages [19]. Immunosenescence encompasses progressive dysfunction of both humoral and cellular immune functions contributing to increased host susceptibility to TB [20]. Therapeutic failure among older patients may be due to decreased absorption of drugs associated with age-related physiological changes such as altered gastric pH, modified gastric emptying rate, and slower intestinal transit time; or it can be related to drug intolerance with polytherapy [21].

Table 2 – Factors associated with the therapeutic failure of pulmonary tuberculosis among the study population with pulmonary tuberculosis (*n* = 231).

	No therapeutic failure (*n* = 163)	Therapeutic failure (*n* = 68)	*p*
Age (⩾40 y)	25 (15.3)	37 (54.4)	.001*
Gender (male)	97 (59.5)	36 (52.9)	.826
Residence (rural)	108 (66.3)	51 (75)	.293
Hookworm infection	17 (10.4)	21 (30.9)	.003*
Corticosteroids (long-term use)	30 (18.4)	20 (29.4)	.036*
Proton pump inhibitors (long-term use)	31 (19)	17 (25)	.059
Chronic obstructive pulmonary disease	37 (22.7)	23 (33.8)	.040*
Congestive heart failure	12 (7.4)	9 (13.2)	.025*
Obesity	29 (17.8)	14 (20.6)	.301
DM	39 (23.9)	25 (36.8)	.021*
Renal insufficiency	17 (10.4)	8 (11.8)	.514
Liver cirrhosis	23 (14.1)	13 (19.1)	.337

Note. All values are given as *n* (%).
DM = diabetes mellitus; *n* = number; TB = tuberculosis.
* Statistically significant.

Table 3 – Predictors of the therapeutic failure for pulmonary tuberculosis among the study population with pulmonary tuberculosis (*n* = 231).

	OR	95% CI	*p*
Age (⩾40 y)	8.4	1.7–41.3	.009*
Hookworm infection	7.6	1.2–49.9	.034*
DM	5.9	1.2–28	.027*

CI = confidence interval; DM = diabetes mellitus; *n* = number; OR = odds ratio; TB = tuberculosis.
* Statistically significant.

It was reported that DM is a predictor of the therapeutic failure of pulmonary TB by Choi et al. [17] (OR 2.52; 95% CI 1.27–5.01), Hongguang et al. [22] (OR 6·7; 95% CI 2–22.2), and Mi et al. [23]. Experiments tracking the immune response weekly showed lower gamma-interferon levels in the lungs of diabetic mice at the critical 2-week time point when the lung Mtb load is rising logarithmically after low dose aerosol challenge [24]. Diabetics had lower plasma levels of interleukin (IL)-22 than nondiabetic TB patients. The potential significance of reduced IL-22 in TB is unknown, but lower IL-22 was linked to impaired pulmonary epithelial barrier integrity with *Klebsiella pneumoniae* infection [25]. In addition, peripheral blood monocytes from patients with DM (type-2) have a reduced capacity to bind or ingest Mtb bacilli compared to monocytes from euglycemic controls. This phenotype was associated with poor glycemic control, and is attributable to alterations in the complement pathway of opsonization rather than monocyte phagocytic ability per se [26].

Hookworm infection was found to affect 16.5% of our study population with pulmonary TB. This rate is lower than that reported by both Elias et al. (28.3%) [27] and Abate et al. (25%) [28] among the patients with TB. The outcome of Mtb infection depends on the cell-mediated immunity. Interaction of macrophages infected with Mtb with both CD4+ and CD8+ T-cells induces the release of cytokines leading to macrophage activation and, in most cases, control of the infection [29]. Individual variation in susceptibility to TB is not fully understood. Protection against TB is associated with enhanced Th1 cell-mediated immune responses [30], while susceptibility to the disease is associated with reduced Th1 type responses and/or enhanced Th2 responses with the resulting high IL-4, IL-5, and IL-10 [31]. Responses of Th2 are usually elicited by helminth infections [32]. It is becoming increasingly evident that helminth infections, in addition to stimulating marked Th2 responses, can induce suppressive T-cell populations known as regulatory T-cells (Tregs) which produce inhibitory cytokines (IL-10 and transforming growth factor-beta) that suppress Th1 responses and interfere with activation of effector T-cells [33]. Such Tregs could be induced to regulate responses to pathogens [34]. Involvement of Tregs in helminth-induced immunosuppression has been reported [35,36].

Our study has some limitations. The sample size is relatively small for extracting solid conclusions. Antimicrobial sensitivity testing was not performed. However, our study has some points in favor. The study is prospective and not a retrospective one. To the best of our knowledge, it is the first study to explore the relationship between hookworm infection and response to therapy of pulmonary TB.

Conclusion

In conclusion, the rate of the therapeutic failure of pulmonary TB is high in Egypt. Besides older age and DM, hookworm infection can reduce the therapeutic response of pulmonary TB. Screening for and control of DM and hookworm infection among patients with pulmonary TB in Egypt may improve the therapeutic response.

Conflicts of interest

The authors have no conflicts of interest to declare.

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