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ORIGINAL ARTICLE

Prevalence of Latent Tuberculosis Infection among patients with Bronchial Asthma Receiving Inhaled or Oral Corticosteroids

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ABSTRACT

Background: Latent tuberculosis infection (LTBI) is extremely high in areas where tuberculosis disease is common and it is used as a reservoir to develop a disease. Inhaled or oral corticosteroids are often used to treat bronchial asthma patients, and that type of treatment can weaken cellular immunity and predispose patients to Mycobacterium tuberculosis infection and reactivation, but in the region, there is insufficient evidence of it.

Hypotheses: To estimate the LTBI prevalence in patients with bronchial asthma using corticosteroids and comparing LTBI prevalence in patients using inhaled corticosteroids (ICS) versus oral corticosteroids (OCS) users.

Methodology: The study was a cross-sectional study carried out at the department of Pulmonology Bacha Khan Medical College, Mardan from January 2023 to June 2023. One hundred adult patients with known bronchial asthma who have been diagnosed with the disease by a physician and have undergone a minimum of four weeks of corticosteroids treatment were enrolled. Participants were divided into ICS and OCS exposed. Symptom screening and chest radiography were used in screening out active tuberculosis. The diagnosis of LTBI was made in the form of tuberculin skin test (positive test 10 mm and above) or interferon-gamma release assay. Demographic factors, the level of asthma, comorbidities, and the pattern of corticosteroids were documented. Chi-square and independent t-tests were used to perform the comparisons with $p<0.05$ as a statistically significant value.

Results: The mean age of participants was 41.6 ± 12.4 years and 58% were female. Sixty patients were receiving ICS only, while 40 had recent or ongoing OCS exposure. LTBI was detected in 28 patients, giving an overall prevalence of 28%. LTBI was significantly more frequent in the OCS group than the ICS-only group (42.5% vs 18.3%, p=0.01). LTBI-positive patients were older than LTBI-negative patients (46.2 ± 11.9 vs 39.7 ± 12.3 years, p=0.02). Diabetes mellitus (35.7% vs 15.3%, p=0.03) and household TB contact (32.1% vs 11.1%, p=0.01) were also significantly associated with LTBI.

Conclusion: LTBI was present in almost one-third of the corticosteroid-treated asthma patients. Exposure to oral corticosteroids, older age, and the history of diabetes and previous TB contact were also risk factors, which indicated the importance of targeted LTBI screening in high-burden settings.

Keywords: Latent tuberculosis; asthma; corticosteroids; prevalence

INTRODUCTION

Tuberculosis (TB) has been one of the most significant public health issues of the world especially in the low- and middle-income countries where the latent tuberculosis infection (LTBI) has contributed to a significant hidden reservoir of tuberculosis disease in the future[1]. LTBI is characterized as an unremitting immune reaction against Mycobacterium tuberculosis antigens with no clinical symptoms of an active infection. It is estimated that a quarter of the global population is latently infected and 5-10 percent of them may develop active TB in their lives particularly with weakening of their immune functions. Considering that high-risk groups are involved in LTBI, identifying them is thus a vital aspect of TB elimination strategies[2]. Bronchial asthma is a chronic inflammatory airway disease that is associated with high morbidity, health care use, as well as poor quality of life in millions of people throughout the world. The mainstay of asthma management is still corticosteroids. Long-term disease control should be done using inhaled corticosteroids (ICS), whereas acute exacerbations and severe refractory cases often require the OCS. Corticosteroids are known to impair cellular immunity especially the functions of T-lymphocytes and macrophage activation which is important in the control of the M. tuberculosis infection despite their effectiveness[3,4]. It has long been identified that systemic corticosteroids were a risk factor in reactivation of latent TB and active disease development. A number of research studies have shown a dose-dependent effect between systemic steroid use and the incidence of TB particularly with long-term exposure[5]. Nevertheless, the preventive effect of inhaled corticosteroids on TB is controversial. Although the ICS are considered to be safer, as they are localized in their effect, in high doses and with extended use they may cause systemic immunosuppressive effects. Even a slight increment in susceptibility in TB-endemic settings may have a significant implication on the public health[6]. Although this is biologically plausible, there are limited data to evaluate the prevalence of LTBI in asthma patients taking corticosteroids especially in South Asian countries where both TB and asthma are very high. The majority of studies available have centered on active TB, and little has been done on the latent infection which is the precursor of active disease and a window of opportunity to fight the disease. Additionally, comorbidities of asthma that may also predispose patients to TB include diabetes mellitus and exposure to smoking[7]. The potential risk population in Pakistan is the group of asthma patients who are prescribed to take repeated courses of OCS or high-dose ICS since TB is endemic in the country. Nevertheless, regular LTBI screening is not a commonly employed method in the management of asthma, mostly because of the lack of local evidence and clear guidelines. It is thus important to understand the burden of LTBI and the risk factors related to it among this population and this information can be used to inform the screening policy and preventive interventions[8]. The paper was aimed to identify LTBI prevalence in bronchial asthma patients undergoing corticosteroid therapy, as well as to compare the frequency of LTBI in patients undergoing inhaled corticosteroid treatment versus patients undergoing oral corticosteroid treatment. The results will give evidence that is more locally relevant to inform clinical practice in risk stratification and LTBI screening implementation in high-burden environments[9].

Study Objectives: To assess the rates of latent tuberculosis infection among patients with bronchial asthma who use corticosteroids and compare prevalence and risk factors of LTBI in patients using ICS and OCS.

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MATERIALS AND METHODS

Study Design & Setting: The study was a cross-sectional study, which was carried out in department of Pulmonology Bacha Khan Medical College Mardan from January 2023 to June 2023.

Participants: One hundred adult patients (aged 18 years and above) with bronchial asthma diagnosed by physicians receiving inhaled and/or oral corticosteroids at least four weeks were enrolled consecutively. The patients were divided into ICS-only and OCS-exposure. Participation was required prior to receiving written informed consent.

Sample Size Calculation: The single-proportion formula was used to calculate the sample size with an estimated LTBI prevalence of 25, 95 per cent confidence level, and 8 per cent margin of error. The sample size of 90 patients was the minimum necessary sample, which was increased by 10 per cent; this gave 100 patients as the final sample.

Inclusion Criteria:

- Age ≥18 years
- Asthma bronchial is diagnosticated by physicians.
- Reciprocating ICS and/or OCS during 4 weeks or more.
- Ready to sign an informed consent.

Exclusion Criteria:

- Active tuberculosis (clinical or radiological).
- Secondary LTBI therapy or current anti-TB treatment.
- Known immunosuppressive disease or other major immunosuppressive conditions (HIV infection).
- Pregnancy
- Failure to do LTBI testing.

Diagnostic /Management Strategy: Symptom screening and chest radiography helped to eliminate active TB. The diagnosis of LTBI was done by tuberculin skin test (≥10 mm) or by interferon-gamma release assay. LTBI-positive patients were advised and referred to TB services where they were evaluated in terms of preventive therapy.

Statistical Analysis: Data Analysis SPSS version 24.0 was used. Means and standard deviation were used to present continuous variables, frequencies and percentages were used to present categorical variables. Appropriate t-tests and chi-square tests, which were independent, were used. A p-value of less than 0.05 was taken to be statistically significant.

RESULTS

A total of 100 bronchial asthma patients were enrolled with a mean age of 41.6 ± 12.4 years; 58% were female. Sixty patients were receiving inhaled corticosteroids only, while 40 had recent or ongoing exposure to oral corticosteroids. LTBI was detected in 28 patients, yielding an overall prevalence of 28%.

Table 1. Baseline demographic and clinical characteristics of study participants

Variable	Total (n=100)	ICS only (n=60)	OCS exposure (n=40)	p-value
Age (years), mean ± SD	41.6 ± 12.4	39.2 ± 11.8	45.3 ± 12.6	0.03
Female, n (%)	58 (58.0)	35 (58.3)	23 (57.5)	0.94
BMI (kg/m²), mean ± SD	26.1 ± 4.3	25.6 ± 4.1	26.8 ± 4.5	0.21
Smoking history, n (%)	22 (22.0)	11 (18.3)	11 (27.5)	0.27
Diabetes mellitus, n (%)	20 (20.0)	9 (15.0)	11 (27.5)	0.11
Household TB contact, n (%)	18 (18.0)	7 (11.7)	11 (27.5)	0.04
Moderate–severe asthma, n (%)	46 (46.0)	23 (38.3)	23 (57.5)	0.05

ICS = inhaled corticosteroids; OCS = oral corticosteroids; BMI = body mass index; TB = tuberculosis; SD = standard deviation.

LTBI prevalence was significantly higher among patients with OCS exposure compared with the ICS-only group (42.5% vs 18.3%, p=0.01). LTBI-positive patients were significantly older than LTBI-negative patients (46.2 ± 11.9 vs 39.7 ± 12.3 years, p=0.02). Diabetes mellitus was present in 35.7% of LTBI-positive patients compared with 15.3% among LTBI-negative patients (p=0.03). A history of household TB contact was reported in 32.1% of LTBI-positive cases versus 11.1% in LTBI-negative cases (p=0.01). There were no significant differences in gender (p=0.42) or smoking status (p=0.18) between the two groups.

Table 2. Corticosteroid exposure profile among asthma patients

Variable	Total (n=100)	ICS only (n=60)	OCS exposure (n=40)	p-value
High-dose ICS use, n (%)	38 (38.0)	21 (35.0)	17 (42.5)	0.44
Duration of ICS (months), mean ± SD	14.6 ± 6.2	13.9 ± 5.8	15.6 ± 6.7	0.19
Recent OCS use (last 3 months), n (%)	40 (40.0)	0	40 (100)	—
Cumulative OCS dose (mg prednisolone-equivalent), mean ± SD	—	—	620 ± 210	—
OCS duration (days), mean ± SD	—	—	18.4 ± 7.3	—

High-dose ICS classified as per GINA equivalent dosing.

Table 3. Association between LTBI and selected risk factors

Variable	LTBI Positive (n=28)	LTBI Negative (n=72)	p-value
OCS exposure, n (%)	17 (60.7)	23 (31.9)	0.01
High-dose ICS, n (%)	15 (53.6)	23 (31.9)	0.04
Diabetes mellitus, n (%)	10 (35.7)	11 (15.3)	0.03
Household TB contact, n (%)	9 (32.1)	8 (11.1)	0.01
Smoking history, n (%)	8 (28.6)	14 (19.4)	0.18

LTBI diagnosed by tuberculin skin test ≥10 mm or positive interferon-gamma release assay.

Table 4. Multivariable logistic regression analysis for predictors of LTBI

Predictor	Adjusted OR	95% CI	p-value
OCS exposure	2.91	1.14 – 7.42	0.02
High-dose ICS	2.10	0.89 – 4.95	0.09
Diabetes mellitus	2.68	1.01 – 7.11	0.04
Household TB contact	3.21	1.18 – 8.71	0.02
Age (per 10-year increase)	1.34	1.02 – 1.77	0.03

OR =odds ratio; CI = confidence interval. Model adjusted for age, sex, smoking history, asthma severity, diabetes mellitus, and household TB contact.

DISCUSSION

LTBI was 28% in this cross-sectional study of 100 adults with bronchial asthma on corticosteroids (LTBI positivity was significantly higher in patients using oral corticosteroids (OCS) than in those using inhaled corticosteroids (ICS) alone (42.5% vs 18.3, p=0.01). Moreover, advanced age, diabetes mellitus, and household contact with TB were found to be significantly related to LTBI[9]. Taken together, these results indicate that overall systemic steroid exposure in asthma, especially in a TB-endemic area may be used to identify a subpopulation of asthmatics with a greater latent TB burden to implement specific screening and preventive measures[10]. The observed overall LTBI prevalence (28%) is interesting considering the relatively younger mean age (41.6 years) of the population compared to many LTBI-screening cohorts in chronic airway disease. Recent studies on the populations of older COPD have established IGRA positivity of approximately one quarter to denote that LTBI is prevalent in chronic respiratory patients despite non-asthma cohorts[11]. The COPD screening study conducted with IGRA-positive rates of 23.8% in 2025 supported the idea that steroid burden is related to the risk of latent TB, with the positive effect of LTBI identified in the use of inhaled corticosteroids and the accumulation of prednisolone equivalent exposure after some threshold[12]. Although COPD and asthma are different in their pathophysiology, the two illnesses are characterized by a common exposure to corticosteroids, frequent healthcare visits, and comorbidities that could be responsible in the occurrence of similarity in the LTBI prevalence estimates[13]. This association to be stronger with exposure to OCS in our cohort is biologically sensible and consistent with the existing literature on systemic glucocorticoids and predisposition to mycobacteria. Systemic corticosteroids inhibit cell-mediated immune response, destabilize macrophage activation, and down-regulate cytokine signaling that is imperative to TB containment, and as a result, enhance the probability of acquiring and/or developing latent TB into active disease[14]. Recent reviews- such as those that have been published in the past five years on the subject of steroid-associated TB reactivation in high-risk settings- still reinforce the

idea that, even comparatively brief courses of systemic steroids can still be temporally related to TB reactivation in susceptible persons[15]. Despite the increased number of such reports addressing active TB as opposed to LTBI detection, the dose exposure model is similar to our finding that the most apparent difference in the prevalence of LTBI between groups was with regard to systemic steroid exposure (an easily measured clinical variable)[16]. However, the interaction between ICS and TB is a more subtle one. In 2022, a review of the existing data on clinical commentaries found that the use of ICS in the management of asthma and COPD is linked to a minor but significant risk of pneumonia and TB, and thus clinical attention should be paid to these phenotypes[17]. Notably, the extent of risk seems to be dose- and context-related: increased ICS doses, increased duration, and simultaneous systemic steroids can make an individual more vulnerable[18,20]. This interpretation model best fit on our data where ICS-only users were found to be less LTBI positive and a significant burden of LTBI persisted in the ICS-only group- probably due to high background exposure in the community and heterogeneity concerning dose and duration of ICS exposure[18]. This biologic gradient is also evidenced by mycobacterial outcomes other than TB; recent studies have also correlated exposure to ICS in chronic airway disease with a higher risk of nontuberculous mycobacterial infection particularly at higher dosage and in older patients, which may also indicate class-related immunologic consequences that can be readily extrapolated to TB in the setting of endemicity[19]. The strong correlations between diabetes and household TB contact and LTBI in our cohort are in line with the existing epidemiology and support the idea of risk stratification[20]. Household contact is an immediate indicator of the possibility of transmission, and diabetes weakens innate and adaptive immunity and gains more and more commonness in adult patients with asthma, which makes the cases more vulnerable in case of constant prescription of systemic steroids. Clinically, converging risk determinants would imply that an empirical screening approach in the TB-endemic countries would focus on asthma patients who have been subjected to OCS in the recent past, especially those who are older, diabetic, or those who have had contact with TB, as opposed to screening all ICS users. Future multicenter prospective cohort studies must estimate dose response (accumulated OCS exposure and high dose ICS groups) and whether targeted LTBI screening and preventive treatment decreases the following active TB in asthma populations.

Limitations: The limitation of the study was the cross-sectional design, which does not allow causal inference on the LTBI and corticosteroid exposure. The duration and dose of the steroids were part of the recall of the patients, and it could be associated with bias in the information. It is a small-scale study on the single-center and therefore, the results are not likely to be applicable to all asthma populations.

CONCLUSION

Latent tuberculosis infection was prevalent in patients with bronchial asthma under corticosteroids, especially those exposed to oral treatment. Age, diabetes mellitus and previous household contact with TB were also risk factors that enhanced LTBI. Repeated or sustained corticosteroid use in the systemic setting ought to prompt targeted LTBI screening prior to its use.

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