

Analysis of Tuberculin Skin Test in Adult Asthmatic Patients Using Steroids as Part of Their Management

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Abstract

Background: Tuberculosis infection being one of the major risk factor for morbidity and mortality in developing countries according to WHO and CDC. The risk of developing TB increases significantly with the drop of immunity.

Using steroid (prednisolone or its equivalent) at a dose of more than 15 mg/day more than 4 weeks is associated with significant drop in immunity, hence increasing the risks of being infected with TB to eight folds

Aim of the Study: To assess the risk of developing TB infection in asthmatic patients that use steroid in their asthma treatment regime.

Materials & Methods: A prospective study designed to include patients complaining from Asthma who have visited Baghdad teaching hospital in the period from (June 2016 to June 2017) that included in-patients and out-patients.

A questionnaire prepared to document the related information of most concern to the researcher and for the sake of study.

Results: In this study, we managed to enroll 60 patients. Male to female ratio was 7:23. 80% of the study cohort lived in urban residence and 20% in suburban neighborhood. 33.3% of the patients had diabetes as comorbidity. 21.7% of the patients used inhaled steroid as a modality of management of asthma, while 45% used systemic steroids, and 33.3% used combined modality. Of the study cohort, 18.3% used steroid for no more than 4 weeks, and the rest used it for more than 4 weeks. Regarding tuberculin test results, 11.7% test positive.

A significant correlations were found between the tuberculin test and the increasing age of the patient $p=0.01$, and the duration of use of steroids $p=0.001$, also, between TST and previous history of TB $p=0.04$.

Conclusion: There is no relationship between the type of steroid and the risk of getting TB infection.

The risk of steroid on immune system and the raise of risk increase with increasing subject age. The extended period of exposure to steroid will definitely increase the risk of TB infection.

Keywords: asthma, tuberculin skin test, steroids

1. Introduction

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, including mast cells, eosinophils, T lymphocytes macrophages, neutrophils, and epithelial cells. In susceptible individuals, inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning (NJIRA 2015).

1.1 Role and Types of Steroids in the Management of Asthma

1.1.1 Inhaled Corticosteroids

With recognition of the central role of inflammation in the pathophysiology of asthma, contemporary treatment

strategies now emphasize inhaled corticosteroids for long-term control of symptoms. Corticosteroids suppress inflammatory responses through a broad expression influence on signal transduction and gene expression pathways (GINA, 2017). Corticosteroids bind to a specific cytoplasmic receptor that translocate to the nucleus, where it modulates expression of inflammatory genes through inhibition of histone acetyl transferase's and recruitment of histone deacetylases, two classes of histone modifiers that control DNA unwinding and gene expression epigenetically (Adcock, 2004; Barnes, 2006).

Airway inflammatory cell influx and markers of airway inflammation in asthma are reduced by corticosteroid administration (Van Rensen, 1999; Olivieri, 1997).

1.2 Systemic Corticosteroids

Systemic corticosteroids have been used in the treatment of asthma since the 1940s and continue to be a cornerstone of the management of acute exacerbations. However systemically administered corticosteroids are associated with a variety of undesirable side effects. The introduction of ICSs in the 1970s ushered in a new era in the treatment of asthma. As with bronchodilators, delivery of drug directly into the lungs through the use of inhaled preparations minimizes systemic toxicity and improves therapeutic benefits. The use of ICSs improves all aspects of asthma control; ICSs reduce asthmatic symptoms, improve lung function decrease airway inflammation, and control AHR (Juniper, 1990; The Childhood Asthma Management Program, 2000).

1.2.1 Tuberculin Skin Test

In 1891, Robert Koch discovered that components of *Mycobacterium Tuberculosis* in a concentrated liquid culture medium, subsequently named "old tuberculin" (OT). Where capable of eliciting a skin reaction when injected subcutaneously into patients with Tuberculosis.

In 1932, Seibert & Munday purifies this product by ammonium sulfate precipitation to produce an active protein fraction known as "tuberculin purified protein derivative" (PPD). In 1941, PPD-S developed by Seibert and Glenn, was chosen as the international standard. Later the WHO, and the UNICEF, sponsored large scale production of a master batch of PPD (RT23) and made it available for general use. The greatest limitation of PPD is its lack of *Mycobacterium* species septicity, a property caused by the large number of protein in this product that are highly conserved in the various species.

Skin test with tuberculin-PPD (TST), is most widely used in screening for (*M. Tuberculosis* infection) (LTBI). The test is of limited value in the diagnosis of active TB because of its relatively low sensitivity and specificity and its inability to discriminate between latent infection and active disease.

False negative reaction is common in immune suppressed patients and in those with overwhelming TB infection. False positive reaction may be caused by infection with the non-tuberculosis *Mycobacterium*, and by BCG vaccination (Centre for disease Control & Prevention, 2016). Corticosteroid through their immunosuppressive and anti-inflammatory effects, impair antibody formation and cell mediated immunity (Fine, 1990). Through these action, steroid predispose patients to a variety of secondary infections including; reactivation of latent Tuberculosis foci, and re infection with *Mycobacterium tuberculosis* (Dharam, 2002). These effects are more evident if steroid dose exceed 0.03 mg/kg/day of prednisolone or equivalent. At a dose higher than 1 mg/kg/day, a marked increase in the susceptibility to wide variety of infection is experienced after several weeks. Treatment for less than 5 days appears to have less effect on immune function (Schaaf, 2010).

1.3 Aim of Study

This study was designed to:

Elucidate the relationship between the use of steroid in adult asthmatic patients and the risk of development of Latent Tuberculosis infection.

2. Patients and Methods

A prospective study designed to include patients complaining from Asthma proved diagnosis according to GINA guidelines who have visited Baghdad teaching hospital in the period from (June 2016 to June 2017) that included in-patients and out-patients.

A questionnaire prepared to document the related information of most concern to the researcher and for the sake of study, post-verbal and written.

2.1 Inclusion Criteria

1). Asthmatic patient older than 18 years old.

2). Patients should be on steroid as one of the management of asthma regardless of the type nor the brand or the manufacturer.

3). Patients have to be on steroid for at least 4 weeks not less than that.

2.2 Exclusion Criteria

1). Patients with active TB, or on anti-TB medication.

2). Asthmatic patients, on steroid as a management of asthma but earlier than 4 weeks.

At the moment patient included to the study cohort, his relevant information where reported regarding asthma including; history of asthma, duration since diagnosis, medication used, steroid type and duration.

En suite, patients' examination including thorough systematic exam to full chest examination and data recording. A diagnostic test was sent including Pulmonary Function Test (PFT), and the Bronchodilatation Reversibility test.

History of steroid use was so important that special inspection and we stressed on the duration of use regardless of type or dosing scheme.

Tuberculosis Bacillus infection (TB) took its share in the quest, as any patients who reported a minor relation to TB was excluded from the study. An entailed TB history if any or a recent or past use of anti TB medication. We used PFT and the Reversibility Test to determine the accuracy of our diagnosis of asthma, also Sputum for Acid Fast Bacilli (AFB) and sputum culture to eliminate any possibility of TB infection.

A complimentary and any ancillary diagnostic tools were employed including; chest X-ray. A series of lab tests (WBC, ESR) that we could get.

Tuberculin Skin Test was done by injection of purified protein derivatives to the inner surface (volar aspect) of the forearm of the patients under the study and mainly to the left side. The patient is discharged home after marking the site of injection and instructed to be back in 48-72 hours for data recording.

The induration that ensues and not the redness that took our attention. A positive test is when the induration is more than 5 mm in immune compromised patients; this is according to the most recent report of CDC regarding HIV and TB, and an induration of more than 14 mm at and around the injection site is considered positive in any person regardless of known risks of TB.

The data after collection were analyzed by the application of chi-square statistical analysis.

3. Results

We have managed to collect and include 60 patients. Of our group, 14 were male and 46 female and a male to female ratio of 7:23

Table 1. Gender distribution

		Frequency	Percent
Valid	male	14	23.3
	female	46	76.7
	Total	60	100.0

Concerning co-morbidity and associated diseases, diabetes was on the top of the list, as 33.3 % (20 patients). Other diseases like hypertension composed 20% of this study group. Table 2 shows co-morbidities of the study group.

Table 2. Co- morbidity diseases

		Frequency	Percent
Valid	DM	20	33.3
	Malignancy	2	3.3
	Other	12	20.0
	Negative	26	43.3
	Total	60	100.0

Steroid use, type and duration were of our top interest in this study. Here in table 3, we show that 21.7% of this study were using inhaled steroid as modality of treatment of asthma, whereas 45% used systemic therapy (as prednisolone tablet or injections), while 33.3% used a combination of inhaled and systemic therapy.

Table 3. Steroid types used in treatment of asthma

		Frequency	Percent
Valid	INHALED	13	21.7
	SYSTEMIC	27	45.0
	COMBINATION	20	33.3
	Total	60	100.0

Table 4 will show the duration of use of steroid in this study, we managed to split patients into four groups according to the duration, first those who used steroid for no more than 4 weeks which represent 18.3% of the fox under study. 43.3% used steroid for period ranging from 5-16 weeks. While 36.7% of this study cohort used it for more than 25 weeks.

Table 4. Steroid use /week

Weeks		Frequency	Percent
Valid	4 or less	11	18.3
	5-16	26	43.3
	17-24	1	1.7
	>25	22	36.7
	Total	60	100.0

Regarding the analysis of tuberculin test results (TST). In this study we relayed on consideration that for the test to be regarded as positive, it should show induration of 5 mm and more to be accepted as a positive feedback after 48-72 hours. Considering that, 88.3% of study group showed negative TST, 6.7% showed induration of 5-14 mm after 72 hours, and 5% showed induration of more than 14 mm. A total of 11.7% returned a positive TST result. Table 5 shows test results.

Table 5. Tuberculin skin test results

		Frequency	Percent
Valid	less than 5	53	88.3
	5-14	4	6.7
	>14	3	5.0
	Total	60	100.0

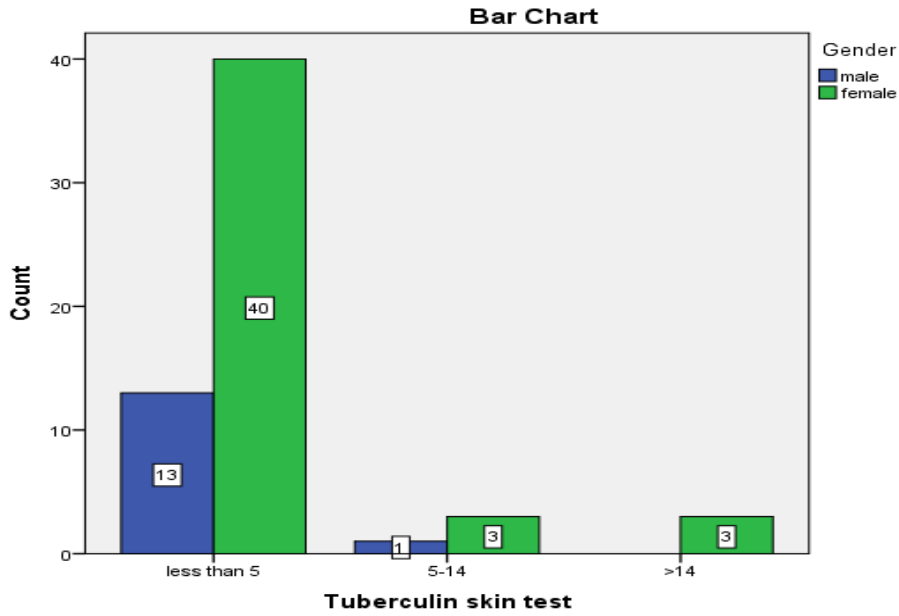


Figure 1. Relation between Tuberculin skin test and Gender P value = 0.61, no significant relationship between TST and gender

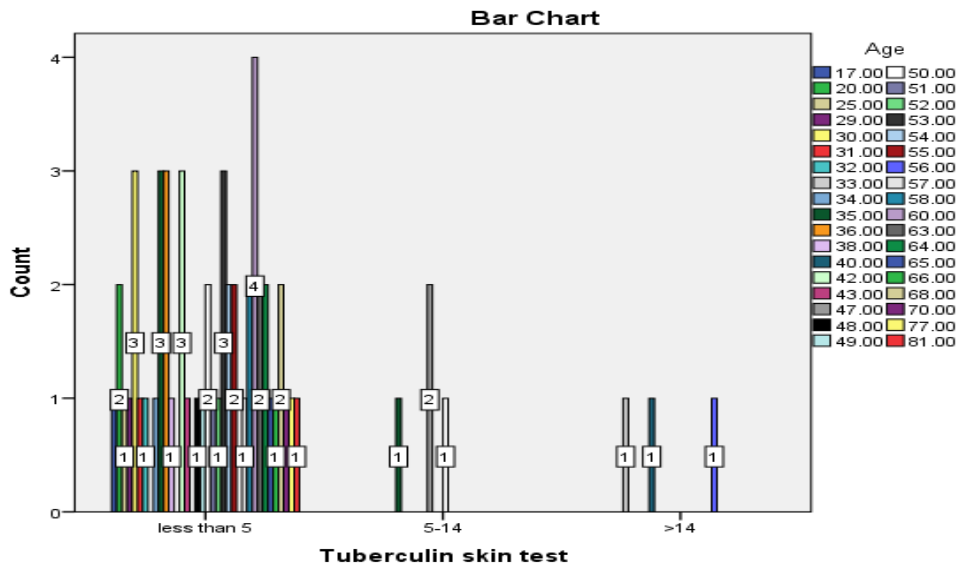


Figure 2. Relation between Tuberculin skin test and Age group P value = 0.01, there is a significant relationship between increasing age and TST

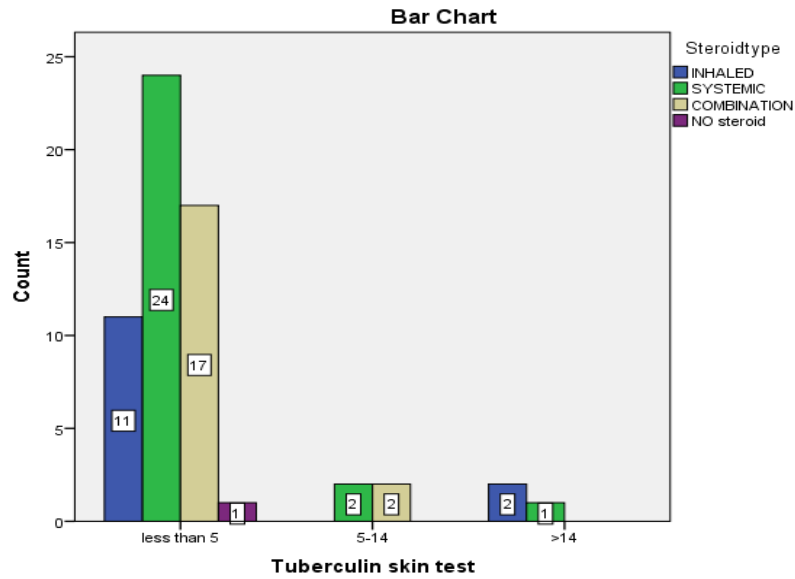


Figure 3. Relation between Tuberculin skin test and Steroid type P value = 0.5. No significant relationship between TST and the type of steroid

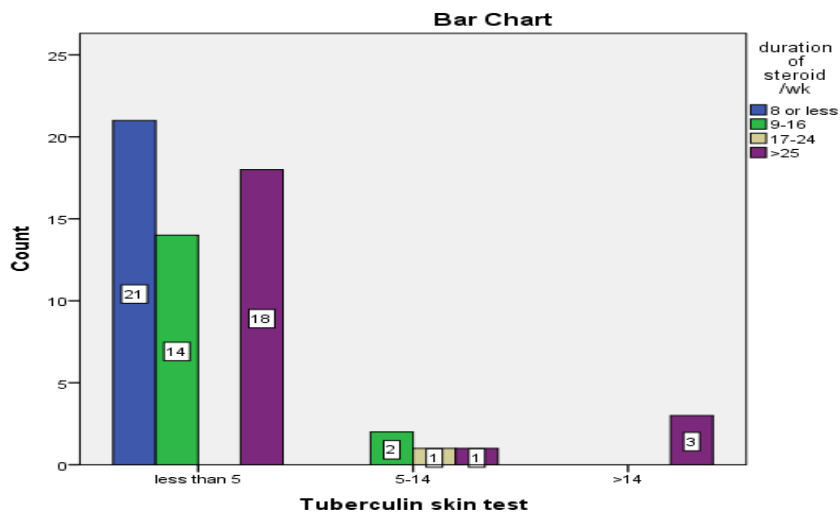


Figure 4. Relation between Tuberculin skin test and duration of steroid/week P value = 0.001. There is a strong relationship between the TST and the duration of use of steroid

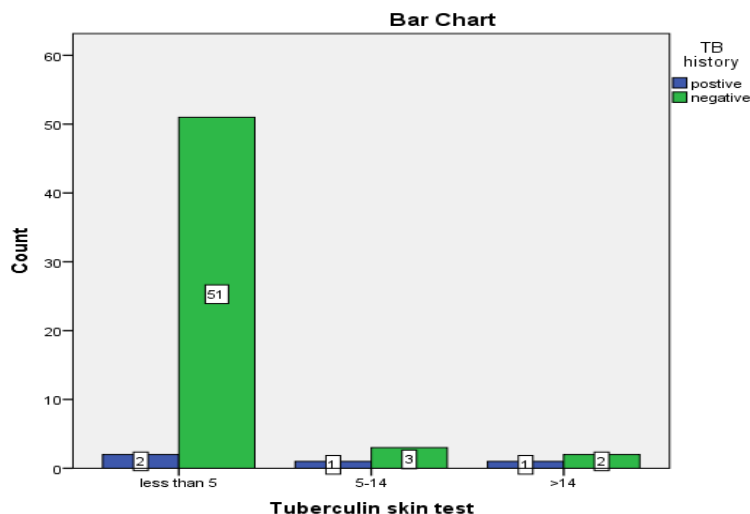


Figure 5. Relation between Tuberculin skin test and tuberculosis history P value = 0.04. There is a strong relationship and history of TB

4. Discussion

By applying the null hypotheses and the p-value relation, and chi-square. There is no statistically significant association between gender and development of TB infection, as p-value was **0.61**.

It has long been recognized that older people are vulnerable to develop tuberculosis (Institute for Health Metrics and Evaluation Global Burden of Disease, 2014). This is widely acknowledged in high-income countries, but rarely considered in developing country settings.

There is statically significant association between age and TST. The p-value was **0.001**, this finding run with the global finding of prevalence and incidence of TB worldwide. A national tuberculosis prevalence survey, conducted in China in 2010, revealed relatively stable and low tuberculosis prevalence rates up to age 40 after which prevalence more than quadruples to age 75. This age-associated increase in tuberculosis incidence was most pronounced in Chinese men. Register-based data from Hunan Province in China showed that the prevalence of tuberculosis was more than twice as high in those aged 65 years as an older as in younger adults (aged 15–64). Older adults in India, which has the highest proportion of tuberculosis cases globally, face further complications due to the presence of drug-resistant strains of tuberculosis. The elderly in some regions in India are estimated to make up 14% of all tuberculosis patients and have a higher likelihood of unfavorable outcomes due to drug-related adverse events, increased co-morbidity, and a higher rate of poverty than younger adults (Marengoni, 2011).

It is not only about relative numbers, older adults tend to be more vulnerable as a group than younger adults. This may be ascribed to compromised immune responses resulting from increased co-morbidity (Riza, 2014), due to a range of chronic diseases (e.g. diabetes or chronic lung disease) and immunosuppressive therapy (with arthritis, organ transplants or cancer etc.), and age-related immune-senescence (Marengoni, 2011).

Our study result analysis report a poor correlation between co-morbidity and TST. Diabetes triples the risk for active tuberculosis, so with rates of diabetes rapidly rising in many tuberculosis endemic areas, it is likely that the present tuberculosis epidemic will be sustained – in particular among older people most affected by diabetes. (Mi, Tan, & Liang, 2013).

Glycemic control, necessary to address diabetes and also to improve tuberculosis outcomes, is particularly challenging in the context of multi-morbidity. Co-infection is associated with poorer treatment outcomes. For example, individuals co-infected with tuberculosis and diabetes in China was 4.5 times more likely to fail treatment than those with tuberculosis only (Bartalesi, 2009).

There is no correlation between the types of steroid used in the course of treatment, with the results of (TST). Actually this result echoes other results of regarding this concern, as no matter the type of steroid used. A study carried out at Florence, Italy, revealed that the proportion of positive scoring for TST was significantly lower in patients on treatment with steroids compared with the proportion of positive results in patients who were not receiving treatment with steroids (NC TB Control Program Policy Manual, Rev. 02/13, 2:4).

North Carolina TB Control Program policy manual states that false negative TST reactions may be caused by high-dose steroids (>15 mg of Prednisone or its equivalent given daily for one month or longer)(Schatz, 1976). Schatz et al. also revealed that in patients treated with daily corticosteroids, tuberculin negativity was associated with a higher dose of corticosteroids (Agarwal et al., 2014).

Among oral corticosteroid user, inhaled corticosteroid use did not increase the risk of TB development, however, among non-user of oral corticosteroid, inhaled corticosteroids use was associated with diagnosis of TB. While in the same article in subgroup analysis according to asthma or COPD; inhaled corticosteroid use dose-dependently increased the risk of TB development among patients with asthma. And oral corticosteroid use also increased the risk of TB development in both groups of patients (Brassard, 2011).

Immunosuppression as defined as a temporal condition of impaired cellular and/or humeral immune function with increased risk for distinct non-opportunistic pathogens (Cohn, 2001). The daily intake of equivalent or more than 10 mg or a cumulative intake of equal or more than 700 mg prednisolone equivalent is the exposure carrying a risk for opportunistic infection including TB. And as mentioned above, that using steroid of more than or equivalent to 15 mg prednisolone for more than 4 weeks is associated with a high risk of dropping of immunity, hence increase the risk of having TB infection.

There was also a significant relationship between inhaled corticosteroid and Mycobacterium in patients who inhaling high dose corticosteroid (Fluticasone more than 500 microgram/day) p- value <0.0001 (WHO, 2017).

In this study we have found a significant relation between the duration of using steroid and the result of TST.

The immunosuppression mainly relates to T- and B- cells as well as macrophage. Gram positive and negative pathogens in addition to Tuberculosis and Fungi are amongst the most common (Cohn, 2001).

In this study we tried to match the finding of relevant diagnostic event with the development of TB, we found that there is no significant correlation between the X-ray finding and the results of TST. This goes absolutely with what the CDC display in their report of 2014 concerning that X-ray could be normal in patient with new TB infection or those with reactivation of latent TB (American Thoracic Society, Centers for Disease Control and Prevention, 2000; Jose, 2006).

5. Conclusion

In asthmatic adult patients who use steroid there is no relationship between the type of steroid and the result of TST.

In asthmatic adult patients who use steroid, there is a significant relationship between the age and the result of TST.

In asthmatic patients who use steroid there is significant relationship between duration of steroid use and the TST results

Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

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