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Serum KL-6 : A Predictive Marker for Post Tubercular Fibrosis

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ABSTRACT

The accurate diagnosis of pleural effusion remains a challenging clinical problem. Medical thoracoscopy has an established role in achieving the aetiology of pleural effusion. Pleural biopsies provide best results, but if cytological results can be shown to give concordant results, therapy can be instituted early.

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Introduction

Tuberculosis, is a common communicable infectious disease caused by various strains of mycobacteria, usually mycobacterium tuberculosis [1]. A limited number of studies have documented that between 30 to 47% of patients treated for pulmonary TB continue to have respiratory symptoms at the end of complete and compliant treatment [2]. Fibrosis in Post tubercular cases is quite remarkable ranging from 40-60% of cases. Biomarkers can serve as surrogate endpoints in clinical trials, and can be used to improve treatment outcome by informing therapeutic decisions for individual patients.

KL-6 is a mucin-like glycoprotein with a molecular weight of 200 kd and extensively expressed on the membrane of regenerating type II pneumocytes [3,4]. It has also been reported that KL-6 induces chemotaxis of human fibroblasts in vitro, suggesting that it may have a pathological role in fibrosing lung disease [3]. This suggests that KL-6 level might have influence on the risk of developing fibrotic disease in tuberculosis.

Method

This was a prospective observational study conducted in the Department of Pulmonary Medicine, Vallabhbhai Patel Chest Institute, Delhi. From October 2016 to April 2018 to correlate levels of serum S.KL-6 with emergence of fibrosis in tuberculosis patients during and after the completion of treatment. 50 patients of newly diagnosed microbiologically confirmed pulmonary tuberculosis patients were recruited after taking written consent.

Patients with any systemic disease or HIV positive patients as well as pregnant and lactating female or patients having past history of tuberculosis or ATT intake and with other pulmonary fibrotic diseases like ILD,CTD-ILD were excluded. 32 healthy matched controls were included in study to know the normal reference range of parameters in Indian scenario.

In this study we collected blood samples before and after the treatment of tuberculosis under DOTS to measure serum KL-6 value. The KL-6 level was measured by a sandwich-type enzyme-linked immunosorbent assay technique using a KL-6 antibody kit as per the manufacturer's instructions and its level was expressed in ng/ml.

A Non contrast HRCT chest scan to notice development of post tubercular fibrosis was done in the suspected case as well as spirometry was done in the patients following 6 months after treatment to correlate the %FVC decrease with serum KL-6.

Data are expressed as mean ± standard error. Comparison between the groups was done using ANOVA (Analysis of Variance) and independent t-test where appropriate and the results obtained were then analyzed. Correlation between variables was estimated using the Spearman rho correlation coefficient. A significance value of $P< 0.05$ was accepted as significant for all the analysis.

Results

A total of 50 patients (mean age 45) and 32 healthy adults (mean age) were enrolled. There was no significant difference in the sex , weight, BMI between the two groups. Out of 50 positive samples for AFB 10 were scanty,24 (48%) was +1 another 10 (20%) were graded as +2 and lastly 6 samples (12%) were graded +3. Serum KL-6 values that were measured pre-treatment were 139.07+-110.85ng\ml jn cases and 20.32+6.46 in controls KL-6 values came significant with p value <0.05 and 95 % confidence lower limit at 79.62 and upper limit at 157.87.

Table 1: Values of S.KL-6 in Case n-50 and Controls n-32 after 6 Months Period

S.KL-6 Values	N	Mean	Std. Deviation	Std. Error Mean
Cases	50	139.07	110.85	15.67
Control	32	20.32	6.46	1.14

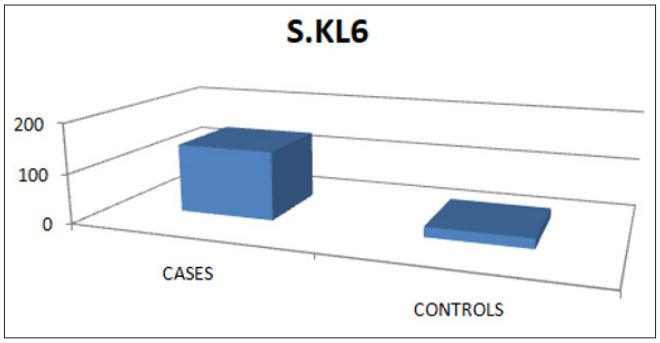

Figure 1: Graph Showing Mean Values of S.KL-6 in Cases and Healthy Controls at the End of 6 Months

Non contrast CT chest was done for all the 50 cases after 6 months of first visit to identify fibrosis. 12 (24%) out of cases(n=50) developed fibrosis post tuberculosis that can be appreciated on NCCT. 10 were having residual symptoms at the end of 6 months of ATT.

Table 2: Fibrosis on CT scan

Fibrosis	Frequency	Valid Percent
Absent	38	76.0
Present	12	24.0
Total	50	100.0

We analyzed the values of S.KL-6 in serum of cases having fibrosis on NCCT (n=12) and those not having fibrosis (n=38), value of KL-6 in cases having fibrosis (n=12) was 298.2± 68.7 whereas, in cases who didn't develop fibrosis values were 88.8±63.64 ng/ml.

Table 3: Showing Mean Values of KL-6 after 6 Months in Cases Having Fibrosis on CT scan (n=12)

Fibrosison CT Scan	N	Mean S.KL-6 Value After 6 Month	Std. Deviation	Std. Error Mean
Present	12	298.27	68.790	19.85
Absent	38	88.80	63.645	10.32

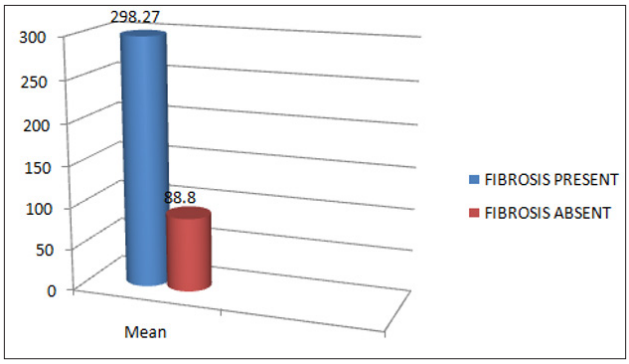

Figure 2: Mean Values in Cases Having Fibrosis (n=12) vs not Having Fibrosis (n=38)

T test application showed there was a mean difference of 209.47 with 95% confidence limit of 162.32 -256.61 with a p value <0.05 which is statistically significant which means there is a strong positive correlation between fibrosis and S.KL-6 value.

We also correlated the difference in the values of S.KL-6 before and after 6 months with patients having fibrosis (n=12) and not having fibrosis (n=32) and found that mean value of change in S.KL-6 values in patients with no fibrosis in CT scan was 14.98 ng/ml whereas, in patients having fibrosis on CT scan it was 221.57ng/ml.

Table 4: Mean Values of Difference in S.KL-6 Values in Cases Having Fibrosis and not Having Fibrosis

FibrosisonCTscan	N	Mean	Std. Deviation	Std. Error Mean
1	12	221.57	58.098	16.77
0	38	14.98	64.89	10.52

It was statistically significant with (p<0.05) whereas in cases not having fibrosis p value was p=0.791 and hence we can say that S.KL-6 values maintained a positive linear relationship with development of fibrosis.

On analyzing the data of difference in S.KL-6 of before and after 6 months with patients having fibrosis on CT scan, we interestingly found that there was a high statistical significance with the difference coming out to be 221.57±58.1 ng/ml but there was almost no difference in the values of patients not having fibrosis on CT scan with 14.9±64.89 ng/ml. with p values <0.05 and >0.05(=0.791) respectively for the two. Thus, we conclude that S.KL- 6 values rises with fibrosis in our study.

Post-bronchodilation mean values for FEV1/FVC in cases were 77.4 ±9.2. Out of 50 cases 13 came out with obstruction (26%). Spirometry with reversibility was performed in all the cases (n=50) after 6 months and forced vital capacity of the cases were compared to confirm the amount of restriction. A median of 80% of predicted with standard deviation of 17.6 was analyzed for cases with a minimum of 45% and a maximum of 111.

Serum KL-6 levels were correlated with both FEV1/FVC and FVC it was found that the p value for correlation was 0.703 for the former therefore the data was statistically not significant and hence no correlation between KL-6 and FEV1/FVC values, whereas there was an inverse monotonic relationship between serum KL-6 values and forced vital capacity in the study cases (n=50) which was statistically significant as p=0.001.

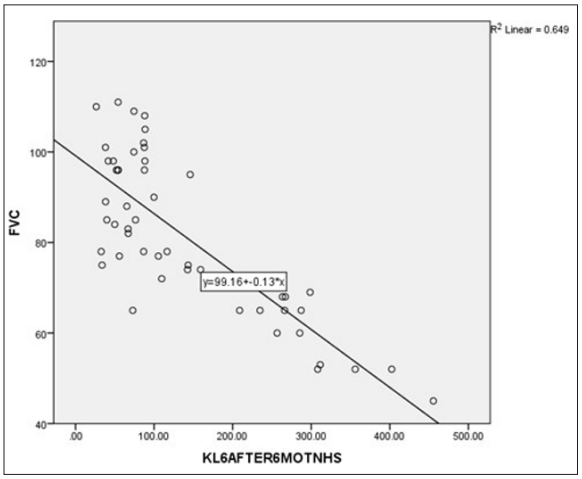

Figure 3: Spearman's Correlation of Serum KL-6 Values with FVC % Predicted

Discussion

Chest abnormalities can suggest pulmonary TB disease. A posterior-anterior radiograph of the chest is the standard view used for the detection of chest abnormalities [5].

Even then, disease activity may not be accurately assessed by radiographs and the frequency of false-negatives is higher in HIV-positive patients [6-8].

The various image findings like consolidation ,which may be upper lower or lobular ,cavity [9-12] . Rim enhancing lesion, cavity which may be thick or thin walled [13,14]. Nodules which may be centrilobular, clustered or miliary [15-17].

A limited number of studies have documented that between 30 to 47% of patients treated for pulmonary TB continue to have respiratory symptoms at the end of treatment, 40% after one year of treatment and 15.9% after two and half years after treatment [18-21].

Pulmonary TB is associated with various long term lung complications including lung scarring (fibrosis), bronchiectasis, Chronic Pulmonary Aspergillosis (CPA), air way stenosis and Chronic Obstructive Pulmonary Disease (COPD) and it may even be a risk factor for lung cancer [22,23]. There is however very limited data on the full spectrum of these complications in cohorts of patients treated for PTB. For many of these complications the published literature is based mostly on case reports and small case series. In one such study, Neeta Singh et al report on 51 multidrug resistant TB patients who were successful treated. Of these, 78% had persistent respiratory symptoms, 98% had residual radiological sequelae, 96% had ventilatory defects with 66% of those with ventilatory defects exhibiting a mixed type of ventilatory abnormality while 19% had pure restriction and 11% had pure obstruction after completion of treatment [23,24].

Rajasekaran et al. analyzed patients with unilateral lung destruction and found pulmonary tuberculosis as the cause in 83.3% of patients (Rajasekaran et al., 1999) [25]. The prevalence of aspergilloma associated with chronic tuberculosis has been reported to be 11% [26,27]. Bronchiectasis is seen in 30%–60% of patients with active post primary tuberculosis and in 71%–86% of patients with inactive disease at high-resolution CT [28-30]. Endobronchial involvement occurs in approximately 2%–4% of patients with pulmonary tuberculosis [31]. Broncho lithiasis is an uncommon complication of pulmonary tuberculosis and is defined as the presence of calcified or ossified material within the lumen of the tracheobronchial tree [32,33]. Scar carcinoma, fibrothorax and spontaneous pneumothorax are amongst other significant post tubercular changes [34-37].

In various studies done for markers in tuberculosis like Study done by Gulhan Cakir et al in 2012 on serum Chitotriosidase levels which correlated significantly with the disease radiologically as well as post treatment scoring [38]. As well as study by Enomto Y et al. stated that the levels of SP-A, SP-D, and CRP reflected positively with disease extent and outcome [39]. Therefore, these biomarkers could be useful for the management of pulmonary tuberculosis. Various studies have been conducted on interferon (IFNγ) inducible protein 10 (IP10) which was found to be increased in the unstimulated plasma of children and adults with active TB and its significance as a marker of tuberculosis in fluids other than blood as well [40-45].

Other markers that have been studied with tuberculosis in various other studies are transthyretin and neoptrin, VEGF, hemeoxygenase-1as wells as markers like ESAT AND CFP in response to tuberculosis therapy [46].

In a study done by Binegdie AB et al. in 2015 stated that out 0f 134 patients' fibrosis was seen in 61% and bronchiectasis in 30% of patients [47]. Similarly, fibrosis was a major complication after the end tuberculosis treatment in a study done by Kim et al in 2001 affecting nearly 40% of the study cases [48]. It's clear that even with proper and regular antitubercular therapy there is no certainty about the disease outcome and as fibrosis is one of the major sequelae in post TB patients therefore there is an eminent need to search test and biomarkers that could help us in predicting these changes.

S.KL-6 has also been studied as a marker for various stages of lung involvement in other diseases like ILDs and it was found that it correlated positively with stages of the disease by degree of lung involvement [49,50]. In our study out of 50 cases at total of 13 cases were reported to have reticular opacity suggestive of fibrosis in their x-rays for which CT scan was being done to evaluate post TB changes out of which fibrosis was present in 12. On examining the values of S.KL-6 in patients having fibrosis to those not having fibrosis we found that value of S.KL-6 in patients with fibrosis was 298.27±68.79 ng/ml where as in patients not having fibrosis it was 88.8±63.64ng/ml these values were modestly statistically significant with p value 0.005(=0.001) .Therefore in conclusion the S.KL-6 values correlate positively with the presence of fibrosis on the CT of the study cases(n=12). Our result was in concordance with various other studies done before. On analyzing the data of difference in S.KL-6 of before and after 6 months with patients having fibrosis on CT scan, we interestingly found that there was a high statistical significance with the difference coming out to be 221.57±58.1 ng/ml but there was almost no difference in the values of patients not having fibrosis on CT scan with 14.9±64.89 ng/ml. with p values <0.005 and >0.05(=0.791) respectively for the two. Thus, we conclude that S.KL-6 values rises with fibrosis in our study.

We reviewed previous published literature and found that Hirasawa Y et al in 1997 An in vitro study of purified S.KL-6 concluded that the biomarker is one of the chemotactic factors for most fibroblasts and that increased S.KL-6 in the epithelial lining fluid in small airways could actually be one cause of the intra-alveolar fibrosis in ILDs [51]. In one Japanese study by Nakajima H et al, of 57 patients with rheumatoid arthritis, 47 with systemic sclerosis, 21 with polymyositis/dermatomyositis, and 18 with systemic lupus erythematosus, S.KL-6 was found to be a useful marker for diagnosis and evaluation of interstitial pneumonia activity associated with collagen diseases [52]. Kobayashi and Kitamura, demonstrated a similar association for S.KL-6 that is increased serum levels of S.KL-6 for sarcoidosis patients with parenchymal disease [53]. Rob janssen et al demonstrated significantly higher levels of S.KL-6 in patients with stage II and III compared to patients with stage I [54]. Interestingly one of the previous study Sakamoto K et al in 2009 demonstrated elevated levels of S.KL-6 elevated in fibrotic nonspecific interstitial pneumonia (NSIP), and were correlated with the extent of fibrotic abnormalities on HRCT, suggesting a value of serum S.KL- 6 as a marker for fibrosis [55].

Altogether, these results strongly suggest that S.KL-6 is a useful marker for determining radiologic disease severity in and it is more likely that it indicates the intensity of on-going fibrosis in pulmonary diseases. Other makers that have been studied for pulmonary fibrosis include SP-A, SP-B by Takahashi et al . Clara cell protein (CC-16), Ca19-9 by Satoha et al and Takayama et al, CK-19 by Fujita et al [56-58].

We observed that there was an inverse monotonic correlation between S.KL-6 values and FVC with more S.KL-6 values in less forced vital capacity (p value<0.001) but there was no any such correlation between S.KL-6 values and FEV1/FVC (p =0.703). Similar results were reflected in study by Inoue et al. in which p<0.05 showing a negative correlation between FVC and S.KL-6 values whereas for FEV/FVC it was not significant with p=0.457 also study by S. Miwa et al also had a negative correlation of S.KL-6 values with %vital capacity (p<0.0001) but did not comment on FEV1/FVC [59,60]. Studies published in other disease having pulmonary fibrosis with PFT correlation tells similar tale, Shirai Y et al in 2015 found that 20 patients who showed sustained increase of S.KL-6 (>500 U/ml) experienced significantly higher %FVC deterioration than those who did not (p = 0.03) [61]. Another study by H Yakamawa et al stated that S.KL-6 correlates with decreased %FVC and DLCO in patients on ILD related to systemic sclerosis and connective tissue disorder [62].

Thus, from the following data we infer that S.KL-6 values are more significant and correlates with the degree of restriction in pulmonary function test. So, we can conclude that S. KL-6 levels were correlating significantly with severity of pulmonary function abnormalities.

Inverse correlation between changes in serum levels of S.KL-6 and pulmonary function tests, suggesting that serial measurements of S.KL-6 may be useful in the follow-up of patients.

The pulmonary function test is non-invasive and easy to repeat but is highly dependent on the patient's cooperation. Instead of frequently repeated pulmonary function tests and radiographic examination, a blood test to follow the course of a patient's disease is easier to perform. But further multicenter studies are needed to confirm this. Although done with full sincerity our study suffered from various limitations like polymorphism mucin -1 568 that is known to influence S.KL-6 levels was not evaluated .as well as the time and patient constraints in this study requires further multicenter validation

Conclusion

In conclusion, Serum KL-6 levels can emerge as a potential biomarker to identify the course of post tubercular fibrosis and airway involvement as it was correlated with HRCT and spirometry findings in our study. So serial monitoring of KL6 may be used to monitor the disease progress with radiological findings and pulmonary function tests although more studies with a larger sample size are required.

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