

Serum neopterin level in cases of pulmonary tuberculosis and pneumonia

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Background Pulmonary tuberculosis (TB) sometimes has diagnostic difficulties and a lot of differential diagnosis such as pneumonia. The aim of this work was to assess the role of serum neopterin in differentiating between pulmonary TB and pneumonia and to estimate the effect of antituberculous drugs for 2 months on serum levels of neopterin in patients with pulmonary TB.

Patients and methods We measured serum neopterin in patients with TB, pneumonia patients, and controls. Serum neopterin was measured again after 2 months of antituberculous therapy in patients with pulmonary TB.

Results Serum neopterin was significantly higher in tuberculous patients than in pneumonia patients, with a sensitivity of 90% and a specificity of 80% at an optimal cut-off value of 20.5 nmol/l. It decreased significantly after 2 months of antituberculous therapy in tuberculous patients.

Conclusion Serum neopterin levels significantly increase in pulmonary TB and correlate with the radiological extent of the

disease. Combined anti-TB treatment decreases the levels of serum neopterin. Measurement of the serum neopterin levels may be useful in following up the drug response in pulmonary TB. Serum neopterin levels may also be helpful in discriminating pulmonary TB from pneumonia.

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Introduction

Tuberculosis (TB) is a chronic specific bacterial infection caused by *Mycobacterium tuberculosis*. It remains one of the deadliest diseases in the world. It is the second leading infectious cause of death after HIV infection [1]. It is an ancient disease with the evidence of the organism being present in skeletons over 4000 years ago [2].

M. tuberculosis is a facultative intracellular pathogen, and macrophages act both as the principal reservoir of infection and as the primary effector cells regulating bacterial growth and viability [3].

Active TB case was confirmed if specimen showed positive acid fast staining for Ziehl–Neelsen (Z–N) or *M. tuberculosis* bacilli was cultured in association with radiographic lesion compatible with active TB on chest radiography, cavities, linear opacity or noncalcified nodules [4].

Pneumonia is commonly defined as an acute infection of the lower respiratory tract. Current approaches to the empirical management of pneumonia emphasize the type of patient, ‘community’ or ‘hospital’, rather than the type of symptoms, ‘typical’ or ‘atypical’ [5].

Neopterin is a pyrazinopyrimidine compound belonging to the pteridine class, which is only produced by living cells [6]. Neopterin is produced

from guanosine triphosphate by stimulated macrophages under the effect of lymphocyte-originated γ interferon. Neopterin is an important marker that plays a key role in the interaction of monocyte/macrophage activation [7].

Neopterin was demonstrated to be a sensitive marker of cell-mediated immune reactions; therefore, the identification of neopterin levels in various body fluids has diagnostic significance in numerous diseases, including the diseases of T-lymphocytes and macrophages [8].

Many authors have studied the role of serum neopterin level in the diagnosis of pulmonary TB, but the role of its serum level in evaluating the response to therapy in pulmonary TB is still an area of investigation [9].

Because of the radiological changes in pulmonary TB and pneumonia, similarity in constitutional symptoms and in some tuberculous cases, and negativity of sputum acid fast stain in some tuberculous cases, the presence of a rapid and accurate test to differentiate both conditions is of critical importance [10].

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The aim of this study was to evaluate the role of serum neopterin level in differentiating between pulmonary TB and pneumonia. The other aim was to estimate the effect of antituberculous drugs for 2 months on the serum level of neopterin in patients with active pulmonary TB.

Patients and methods

This study was carried out during the period from August 2014 to March 2015.

A total of 45 patients (30 patients with pulmonary TB and 15 patients with pneumonia) in addition to 15 apparently healthy controls (age and sex matched) were included in this study.

Participants were classified into three groups.

Group I included 15 apparently healthy nonsmoker volunteers as a control group.

Group II included 30 patients with pulmonary TB diagnosed recently by means of positive Z–N smear.

Group III included 15 patients with bacterial pneumonia who were diagnosed when the patients had clinical signs of pneumonia and a new infiltrate on chest radiography, with negative Z–N smear.

Exclusion criteria

- (1) Cases of multidrug-resistant TB.
- (2) Cases of acute exacerbation of interstitial lung diseases, lung cancer, and pulmonary embolism.
- (3) Increase in liver enzymes to more than three-fold of normal after 2 weeks of starting antituberculous therapy.
- (4) Persistence of sputum positivity for acid fast bacilli after 2 months of antituberculous therapy.

After taking written informed consent and approval of Ethics Committee of Faculty of Medicine, Tanta University, all participants were subjected to detailed history taking, clinical examination, Chest radiography posteroanterior and lateral views, and three sputum samples on three successive days for Z–N staining (for all groups); this was repeated after 2 months of antituberculous treatment for TB patients.

Serum neopterin level was measured for all groups in the beginning of the study, and, for TB patients, the tests were repeated after 2 months of antituberculous treatment. It was measured using a human enzyme-linked

immunosorbent assay using an ELISA kit supplied by DRG Instruments Gmbh (Marburg, Germany).

Tuberculous patients received four drugs during the initial phase of therapy – namely, isoniazide, rifampicin, ethambutol, and pyrazinamide (directly observed treatment, short-course) [11].

After 2 weeks, the liver enzymes (serum glutamic pyruvic transaminase and serum glutamic oxaloacetic transaminase) were measured; if they were less than three times the normal values, the same treatment was continued for 2 months.

Data were analyzed using SPSS (v 15.0; IBM Corp., Armonk, New York, USA). Means with SDs or percentages were used to describe the sample. Student's *t*-test was used to compare the means of two related groups of numerical (parametric) data. The analysis of variance test was used to compare more than two groups of numerical (parametric) data followed by the post-hoc Tukey's test. Intergroup comparison of categorical data was made using the χ^2 -test. The sensitivity and specificity of neopterin to differentiate between TB and pneumonia groups were examined at different cut-off points using Receiver operating characteristic (ROC) curve analysis to determine the best cut-off point as well as the diagnostic power of each test. A *P*value less than 0.05 was considered statistically significant.

Results

During the study period, we recruited 37 patients with active pulmonary TB, of whom seven were excluded (one had marked elevated liver enzymes after 2 weeks and six still had smear-positive sputum samples for acid fast bacilli after 2 months of starting antituberculous therapy). Thus, the remaining 30 patients were included (group II). In addition, 15 patients with pneumonia (group III) and 15 healthy controls (group I) were included.

There were no significant differences among the three studied groups as regards age and sex (Table 1).

Some routine laboratory data of patients in the three groups are shown in Table 2.

Serum neopterin levels before treatment were significantly higher in the tuberculous group than in the pneumonia group, and it was higher in the pneumonia group than in the control group (Table 3).

Serum neopterin levels in tuberculous patients decreased significantly ($P=0.0001$) after 2 months of

Table 1 Comparison among the three studied groups as regards age and sex

	Groups			Test used	P
	Control	TB	Pneumonia		
Age					
Mean±SD	39.00±13.87	43.97±14.40	38.00±11.72	ANOVA	0.3
Sex [n (%)]					
Male	10 (66.7)	22 (73.3)	8 (53.3)	χ^2	0.4
Female	5 (33.3)	8 (26.7)	7 (46.7)		

ANOVA, analysis of variance; TB, tuberculosis.
 $P < 0.05$ is considered significant.

Table 2 Comparison among the three studied groups as regards some laboratory findings

	Groups			P	P ₁	P ₂	P ₃
	Control	TB	Pneumonia				
WBCs							
Mean±SD	8.51±0.95	9.71±3.11	16.83±3.43	<0.0001*	0.3	<0.0001*	<0.0001*
ESR First hour							
Mean±SD	10.27±3.83	98.17±23.49	71.67±7.87	<0.0001*	<0.0001*	<0.0001*	<0.0001*
ESR Second hour							
Mean±SD	20.20±4.90	125.37±20.61	110.87±16.67	<0.0001*	<0.0001*	<0.0001*	0.025*
CRP							
Mean±SD	1.61±0.60	8.42±2.31	40.07±12.16	<0.0001*	0.003*	<0.0001*	<0.0001*

Test used: ANOVA followed by post-hoc Tukey's test.

ANOVA, analysis of variance; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TB, tuberculosis; WBC, white blood cell.

P₁:significance between groups I and II.

P₂:significance between groups I and III.

P₃:significance between groups II and III.

* $P < 0.05$ is considered significant.

antituberculous therapy from 38.64±11.11 to 10.18±1.88 nmol/l. The post-treatment values of serum neopterin in TB patients were significantly higher than that in the control group ($P=0.0001$) and significantly lower than that in pneumonia patients ($P=0.001$).

Among the 30 tuberculous patients, there were seven patients (23.3%) with minimal changes in chest radiography, 14 patients (46.7%) with moderately advanced changes, and nine patients (30.0%) with far-advanced changes.

Table 4 shows the comparison between neopterin serum levels before and after 2 months of antituberculous therapy as regards radiographic changes.

The ROC curve was plotted to determine the cut-off value for serum neopterin in tuberculous and pneumonia patients before treatment (Fig. 1). The cut-off value of serum neopterin was 20.5 nmol/l. The sensitivity was 90.0%, specificity was 80.0%, positive predictive value was 90%, and negative predictive value was 80%, and the accuracy was 86.7%. The area under the ROC curve was 0.962.

Discussion

In our study, age and sex were matched in the studied groups, and hence they were not contributing factors in the differences of serum neopterin levels among these groups.

In the present study, serum neopterin levels were significantly higher in the tuberculous group than in the pneumonia and the control group. They were significantly higher in pneumonia patients compared with controls.

In accordance with these findings, Immanuel *et al.* [12] showed that the serum neopterin levels were higher in patients with active TB than in the healthy control group.

In agreement with these findings, Mohamed *et al.* [13] showed that the serum and bronchoalveolar lavage (BAL) levels of neopterin were found to be higher in advanced TB patients than in healthy individuals.

Moreover, in accordance with our findings, Yuksekol *et al.* [14] reported that the neopterin levels in serum and urine samples of patients with TB were significantly higher compared with patients with lung cancer,

Table 3 Serum neopterin levels in the three studied groups

	Groups			<i>P</i>	<i>P</i> ₁	<i>P</i> ₂	<i>P</i> ₃
	Control	TB	Pneumonia				
Neopterin (nmol/l)							
Mean±SD	3.94±1.72	38.64±11.11	14.5±6.4	0.0001*	0.0001*	0.004*	0.0001*

Test used: ANOVA followed by post-hoc Tukey's test.

ANOVA, analysis of variance; TB, tuberculosis.

*P*₁:significance between groups I and II.

*P*₂:significance between groups I and III.

*P*₃:significance between groups II and III.

**P*<0.05 is considered significant.

Table 4 Comparison between neopterin values before and after treatment in TB patients as regards radiographic changes

	Radiography changes			<i>P</i>	<i>P</i> ₁	<i>P</i> ₂	<i>P</i> ₃
	Minimal	Moderately advanced	Far advanced				
Neopterin before treatment							
Mean±SD	21.78±4.42	39.21±7.32	45.58±9.20	0.0001*	0.001*	0.0001*	0.12
Neopterin after treatment							
Mean±SD	8.86±0.99	9.85±1.99	11.21±1.59	0.04*	0.5	0.046*	0.14

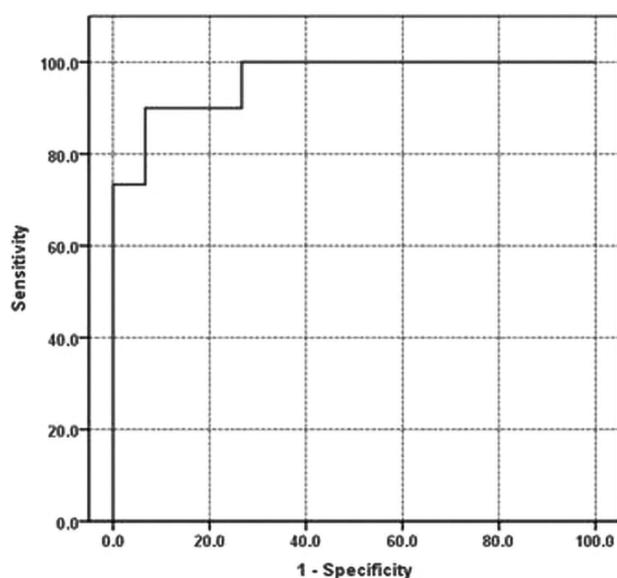
Test used: Analysis of variance followed by post-hoc Tukey's test.

*P*₁:significance between minimally and moderately advanced.

*P*₂:significance between minimally and far advanced.

*P*₃:significance between moderately advanced and far advanced.

**P*<0.05 is considered significant.

Figure 1

Receiver operating characteristic curve analysis showed the serum neopterin level for differentiating between tuberculosis and pneumonia.

pneumonia, and the healthy control group. Secretion of the neopterin by the kidneys was the main reason for this significant difference. They showed that the neopterin quantification in various body fluids, especially in the urine and serum, will be a rapid diagnostic method for TB in the future. They suggested that the measurements of neopterin levels in pulmonary TB patients might reflect disease activity earlier than cultures.

Moreover, Berktaş *et al.* [15] showed that the mean serum neopterin levels were higher in patients with active TB compared with healthy individuals. It represents a sensitive marker for activated cell-mediated immunity. It is produced by human macrophages specifically on stimulation with interferon- γ . The key pathogenetic mechanism in pulmonary TB is the activation of T-cells and macrophages.

Turgut *et al.* [16] also showed in their study that the serum levels of neopterin and interleukin-2 in patients with active TB were significantly higher compared with patients with inactive TB and controls. High levels of neopterin, of which the main source is activated macrophages, demonstrate the importance of the cellular immune response in TB.

Our results also matched with those of Guler *et al.* [17], who showed that the serum neopterin levels were significantly higher in active TB.

Ozdemir *et al.* [18] also found that the serum levels of neopterin in patients with TB were significantly higher than that in controls.

In accordance with our findings, Esma *et al.* [19] showed that the mean value of serum neopterin levels before treatment was higher in the tuberculous group than in the pneumonia and control groups. They mentioned that

the serum neopterin levels may also be helpful in discriminating pulmonary TB from pneumonia.

Salih *et al.* [20] showed elevated neopterin levels in patients with pulmonary TB.

Moreover, we found that serum neopterin levels decreased significantly in tuberculous patients after 2 months of antituberculous therapy.

In accordance with these findings, Immanuel *et al.* [21] showed that all patients with active pulmonary TB had elevated levels of serum neopterin at pretreatment, which had declined at 1 month and were near normal at the end of treatment, and the mean decrease was 37% at 1 month and 66% at the end of treatment. It continued to fall after completion of therapy in patients who did not relapse, whereas an increase after completion of therapy was associated with bacteriologically proven relapse.

Berkas *et al.* [15] found that the measurements of serum neopterin levels in 18 active TB patients at the initial phase and during the second month of therapy showed an apparent decrease in neopterin after treatment.

Moreover, our study is in agreement with the study by Immanuel *et al.* [21], who showed that the serum neopterin levels in HIV-seropositive and HIV-seronegative patients with TB were higher than that in the control group. In HIV-seropositive patients with CD4 less than 200/mm in the peripheral blood, these levels were higher before treatment and decreased more markedly during treatment. Thus, they proposed that measurement of neopterin level can also be used as a technically easy and cheap test, particularly for the early diagnosis and treatment of TB in immunocompromised patients.

In accordance with these findings, Guler *et al.* [17] showed in their study on 40 newly diagnosed patients that pretreatment neopterin levels were found to be significantly reduced in the second month of the treatment. They reported that neopterin levels were safe immunologic markers to evaluate the activation status and treatment response of the TB patients. They showed that the neopterin levels correlated with the extent of pulmonary TB and decreased at the second month of therapy. They reported that the serum neopterin levels were significantly higher in active TB, and the measurement of this biomarker may be useful for measuring disease activity and for following up the treatment of TB.

Turgut *et al.* [16] showed that the neopterin levels were higher in patients with active TB than in healthy controls. These values declined with therapy to the levels similar to those of the healthy control group after treatment of 6 months. Serum neopterin levels in tuberculous patients decreased steadily from the baseline point to the end of antituberculous therapy; this diminution was more prominent in patients with moderately severe TB.

In accordance with our findings, Gordeuk *et al.* [22] found that the serum neopterin levels increased at the initiation of the treatment and decreased significantly at the end of the treatment.

Esma *et al.* [19] and Salih *et al.* [20] showed that the serum neopterin levels decreased in patients with pulmonary TB after 2 months of treatment, and concluded that the neopterin level is a useful marker in the diagnosis and follow-up of TB.

In our work, there was a statistically significant difference among the three radiological categories of tuberculous patients (minimal, moderately advanced, and far advanced) as regards the neopterin values before treatment and after treatment. This indicated a significant correlation between radiological extent of the disease and the serum level of neopterin among tuberculous patients.

Fuchs *et al.* [23] also reported similar relationship and mentioned that this may be explained by local cellular immunity activation.

Moreover, Sodhi *et al.* [24] showed that M. TB-induced IFN- γ production by peripheral blood mononuclear cells correlated with radiographic findings.

Tsao *et al.* [25] showed that in the tuberculous group, patients with far-advanced disease had higher levels of neopterin in both BAL and serum than did patients with moderately advanced or minimally advanced disease.

In accordance with these findings, Immanuel *et al.* [21] showed that patients with limited lesions had the lowest neopterin level. The explanation was that the limited lesions were small, and hence the bacterial load and the antigenic challenge was likely to be low; thus, the activation of the immune system was not enough to produce higher levels of serum neopterin.

In accordance with these findings, Guler *et al.* [17] showed that neopterin levels also correlated with the extent of pulmonary TB.

In contrast, Mohamed *et al.* [13] reported that there was a nonsignificant elevation in the serum, BAL, and serum/BAL neopterin ratio in far-advanced and moderate lesions than in minimal lesions.

In our study, ROC curve analysis showed that serum neopterin level had a sensitivity of 90% and a specificity of 80% for differentiating between TB and pneumonia at an optimal cut-off value of 20.5 nmol/l. The area under the ROC curve was 0.962.

In accordance with these findings, Tozkoparan *et al.* [9] showed that the sensitivity of serum neopterin in pulmonary TB was 85% and its specificity was 93%.

However, Cok *et al.* [26] showed in their study that the sensitivity and specificity of neopterin were 44 and 85%, respectively.

Limitations of our study included noninclusion of drug-resistant tuberculous cases. The few number of this category of patients discourages us to include them as this can disrupt statistical comparison and give odd results. Another limitation is the use of only the serum level of neopterin and not including pleural or bronchoscopic samples. This is because we wanted to have a rapid and noninvasive way to differentiate TB from pneumonia and follow-up treatment response.

Conclusion

Serum neopterin levels significantly increase in pulmonary TB and correlate with the radiological extent of the disease. Combined anti-TB treatment decreases the levels of serum neopterin. Measurement of the serum neopterin levels may be useful in following up the drug response in pulmonary TB. Serum neopterin levels may also be helpful in discriminating pulmonary TB from pneumonia.

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Conflicts of interest

There are no conflicts of interest.

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