Assessment of serum immunoglobulin   and complement components level in patients with pulmonary tuberculosis

Imad A.J Thanoon*,   Hani M. Salih, Suhair M. Rashees***

*Department of Pharmacology, **Department of Pharmacology.
***Department of Clinical Pharmacy, College of Pharmacy University of Mosul

ABSTRACT

Objective: To assess , the serum levels of immunoglobulin IgG, IgM, IgA and , complement C٣ and C٤ in patients with pulmonary tuberculosis at diagnosis and ٣ months after therapy in comparison to age- matched healthy controls.

Methods: This case-control study was conducted at the Advisory Clinic for Chest and Respiratory Diseases at AL-Fasalaa in Mosul City and the Department of Pharmacology –College of Medicine University of Mosul during the period from December ٢٠٠٧ to April ٢٠٠٨. Forty newly diagnosis patients with pulmonary tuberculosis were included in this study , with ٥٠ apparently healthy age-matched subjects taken as a control . Initially from both the patients and the control group , blood sample were taken and assay of serum immunoglobulin levels (IgG, IgM, IgA) and complements (C٣, C٤)   was   done using single radial immunodiffusion method using commercial kits. After ٣ months of therapy another blood sample was taken from the patients group and assay of the same parameters was done .

Results :Initially , there was a highly significant increase in the serum levels of IgA, IgM, IgG and complement C٣ in patients with active pulmonary tuberculoses with insignificant differences in the C٤ levels in comparison to controls .

 After ٣ months of therapy there was a significant reduction in the serum levels of IgM , C٣ with insignificant reduction in IgG, IgA and C٤ concentration in comparison to pre- therapy stage . In addition there was a significant differences in the serum levels of IgA,   IgG, C٣ in comparison to controls .

In conclusion Tuberculosis as a disease and anti- tuberculous therapy do affect the immune system as reflected by the serum immunoglobulin IgA, IgM, IgG and complements (C٣, C٤) levels.

:Keywords: pulmonary T B, immunoglobulin IGG, IGA, IGM, complements (C١,C٢)

الخلاصة

تحديد المستوى المصلي للكلوبيولينات المناعية والمتممات في مرضى التدرن الرئوي

اهداف البحث : لتحديد مستوى الكلوبيولينات المناعية   IgA, IgM, IgG والمتممات نوع C٣, C٤ في مصل دم مرضى التدرن الرئوي عند التشخيص وبعد ثلاثة اشهر من تلقي العلاج بالمقارنة مع مجموعة الضبط من اشخاص اصحاء من اعمار مقاربة لاعمار المرضى .

التصميم : دراسة عينية مقارنة

مكان اجراء البحث والاطار الزمني :

تم اجراء البحث في عيادة الامراض الصدرية في منطقة الفيصلية في الموصل وفي فرع الادوية كلية الطب – جامعة الموصل للفترة من كانون الاول ٢٠٠٧ م الى نيسان ٢٠٠٨م.

المرضى والطرق المتبعة :

تم في هذه الدراسة ادخال اربعين مريضا مشخص حديثا بالتدرن الرئوي مع ٥٠ من الاشخاص الاصحاء من اعمار واجناس مقاربة اتخذت كمجموعة ضبط . في البداية وللمنتسبين للمجموعتين (المرضى- والضبط) ،تم سحب ٥ مل من الدم الوريدي وتم قياس المستوى للكلوبيولينات IgA, IgM, IgG مع المتممات C٣,C٤باستخدام تقنية خاصة وباستخدام عدد فحص خاصة . وبعد مضي ثلاثة اشهر على العلاج تم سحب ٥ مل من الدم الوريدي لمجموعة المرضى وتم قياس المفردات المذكورة اعلاه .

النتائج : في البداية كانت هنالك زيادة معنوية في مستوى الكلوبيولينات المناعية IgA, IgM, IgG والمتمم C٣ في مرضى التدرن الرئوي بالمقارنة مع مجموعة الضبط .

وبعد تلقي العلاج لفترة ثلاثة اشهر اظهرت الفحوص انخفاضا معنويا في مستوى الكلوبيولين IgM والمتمم C٣ مع انخفاض غير معنوي في مستوى الكلوبيولين IgA, IgG والمتمم C٤ بالمقارنة مع فترة قبل العلاج . وكان هنالك اختلاف معنويا في مستوى الكلوبيولين , IgA, IgG والمتمم C٣ بالمقارنة مع مجموعة الضبط .

الاستنتاج : التدرن الرئوي كمرض والعلاج المضاد للتدرن يؤثر فعليا على جهاز المناعة ممثلا بالتاثير على مستوى الكلوبيولينات المناعية IgA, IgM, IgG والمتممات نوع C٣, C٤.

Tuberculosis (TB) is still a major health problem in most developing countries and its incidence is rising in many developed countries.[1] Humoral immunity has a role to play in host defense against infection, particularly of bacterial origin. The role of humoral response in immunity to tuberculosis is unclear and clinical studies have yielded inconsistent conclusions,[2,3] but recently it has been widely recognized and utilized in serologic diagnostic procedures.[4] Information's regarding immunoglobulin levels in patients with TB is surprisingly scant,[5] and there are only a few reports about the complement components and their important role in the development of immunlogically mediated inflammatory reactions.[6,7] The aim of this study is to evaluate the serum levels of immunoglobulin IgG, IgA and IgM, and complements C٣ and C٤ in newly diagnosed cases with pulmonary TB , initially and after ٣ months of standard first line therapy in comparison to healthy controls.

Patients and Methods

The study was conducted in the Department of Pharmacology College of Medicine and the Advisory Clinic for Chest and Respiratory Diseases at Al-Fasalaa in Mosul city from December ٢٠٠٧ to April ٢٠٠٨. Patients were selected according to certain criteria, which included newly diagnosed patients with pulmonary TB (proved by sputum smear examination and chest x-ray), cooperative and compliant, accepting the follow up period, with no other diseases as hypertension, renal disease, liver disease or diabetes mellitus, and all planned for the same first line antituberculosis therapy.

Out of ٤٣ patients interviewed and examined only ٤٣ included in the study of whom only ٤٠ completed the study. Also, included ٥٠ apparently healthy subjects taken as a control group . Initially from both groups (patients and control), ٥ml of venous blood samples were taken at ١٠AM and assay of serum immunoglobulin (IgG, IgA, IgM), and complements (C٣, C٤) was done by single radial immunodiffusion method,[8] using commercial kits . For the patient's group, after ٣ months of therapy, another blood sample was taken and assay for the same parameters was done.

Each patient under study was given ٤ coated tablets (from Svizera labs, India) in the morning for the initial ٢ months of therapy, and each tablet contained isoniazid (INH) ٧٥ mg , rifampicine ١٥٠mg , pyrazinamide ٤٠٠mg and ethambutol ٢٧٥mg with vitamin B٦ ١٠ mg daily. In the subsequent phase of therapy each patient was given INH ٣٠٠mg and rifampicine ٦٠٠mg with vitamin B٦ ١٠mg .

All values were quoted as mean $\pm$SD and a p- value <٠.٠٥ was considered to be statistically significant. Unpaired t-test   was used to compare   results of patients initially and after ٣ months of therapy with that of the controls . Paired t-test was used to compare results of patients in the pre and post therapy stages.

Results

control group

Fifty-apparently healthy volunteers, were taken as a control group . They were ٣٦ males and ١٤ females, and their ages varied between ٢٠ to ٧٠ years with mean$\pm$ SD of ٤١.٨+ ١٤.٢ years.

Patient group

Forty newly diagnosed patients with pulmonary tuberculosis were included in this study . They were ٢٩ males and ١١ females, and their ages varied between ٢٠ to ٦٨ years with mean $\pm$ SD of ٣٩.٩ $\pm$ ١٣.٤ years .

Pre therapy stage

There was a highly significant increasein the serum levels of IgG, IgA , IgM and C٣ in patients with pulmonary tuberculosis (p<٠.٠٠١) in comparison to controls, while complements C٤ levels showed insignificant difference (Table ١).

Post therapy stage

By comparing values of parameters under study before therapy and ٣ months after therapy there was a significant reduction in the serum levels of IgM and complement C٣ , with insignificant reduction   in the serum levels of IgG, IgA and complement C٤ (Table ٢).

By comparing values of parameters under study in post therapy stage with that of the control   there was a significant differences in the levels of IgG, IgA and complement C٣ with insignificant difference in the levels of IgM and complement C ٤ (Table ٣).

Table ١: comparison of the measured parameters between control and patient with tuberculosis before therapy.

Parameters mg/dl)(	Mean $\pm$ SD		p-value
	Control (n=٥٠)	Pre- therapy Patients (n=٤٠)	
IgG	١٠٤٥+١٠١.٦٦	١٢٥٠+١٣٢.٧٤	<٠.٠٠١
IgA	٢٣٢.٧٨+٢١.٨٦	٢٧٦.٦٧+٢٥.٥٨	<٠.٠٠١
IgM	١٥٩.٧٢+٢٥.٩١	١٨٥.٦١+١٦.٦٧	<٠.٠٠١
C٣	١٩٨.٠٦+١٥.٢٧	٢٠٩.٠٩+١٨.٦	<٠.٠١
C٤	٣٦.٢٥+٤.٨٧	٣٧.٦٧+٥.٦٤	٠.٢٦٧(NS)

Table ٢.: comparison of the measured parameters between patients with tuberculosis before and after therapy

Parameters	Mean ± SD		p-value
(mg/dl)	pre- therapy Patients	post- therapy Patients	
IgG	١٢٥٠.± ١٣٢.٧٤	١٢٠٩.٠٩±١٠٩.٦٧	٠.١٥٩ (NS)
IgA	٢٧٦.٦٧±٢٥.٥٨	٢٦٨.٧٩±١٤.٥٣	٠.٠٨١(NS)
IgM	١٨٥.٦١±١٦.٦٧	١٥٦.٠٦±٢٤.٧٤	<٠.٠٠١
C٣	٢٠٩.٠٩±١٨.٦٠	١٦٦.٣٦±١٥.٥٨	<٠.٠٠١
C٤	٣٧.٦٧±٥.٦٤	٣٥.٩٧±٤.٠٨	٠.١٥٤(NS)

Table(٣ : comparison of the measured parameters between controls and patients with tuberculosis after therapy

Parameters	Mean ± SD		p-value
mg/dl)(	Control (n=٥٠)	Post-therapy Patients (n=٤٠)	
IgG	١٠٤٥±١٠١.٦٦	١٢٠٩.٠٩±١٠٩.٦٧	<٠.٠٠١
IgA	٢٣٢.٧٨±٢١.٨٦	٢٦٨.٧٩±١٤.٥٣	<٠.٠٠١
IgM	١٥٩.٧٢±٢٥.٩١	١٥٦.٠٦±٢٤.٧٤	٠.٥٥١(NS)
C٣	١٩٨.٠٦±١٥. ٢٧	١٦٦.٣٦±١٥.٥٨	<٠.٠٠١
C٤	٣٦.٢٥±٤. ٨٧	٣٥.٩٧±٤.٠٨	٠.٧٩٧(NS)

Discussion

Our data showed a significant increase   in the serum levels of IgG, IgA, IgM   and complement   C٣   in patients with active pulmonary TB before therapy in comparison to controls ,and a significant reduction in the serum levels of IgM and   complement C٣ after   ٣ months of anti TB therapy   in comparison to pre- therapy stage.

Diagnosis   of pulmonary   TB is mainly based upon the clinical, radiological   and bacteriological   evidence,   however,   a serologic   diagnostic   test,   would   have considerable   and obvious advantages ٩. Information with regard the effects of tuberculosis and antituberculosis therapy on immunoglobulins and complements level were scanty,old and with somewhat conflicting data. The first study about the subject came in ١٩٧١ by Alakcon- Sefovia and Fishbein , and there findings indicated a significant raise in   all ٣ types of immunoglobulin (IgA, IgG, IgM)in comparison to healthy controls٤. Wong and Saha (١٩٩٠) , reported a significant increase in the serum levels of IgG and IgM , with no change in the IgA and complement C٣   levels in newly diagnosed cases with pulmonary TB ١٠.

Sharma and Coworkers , in a research concerning   cases with miliany TB, reported a significant raise in the levels of IgG, IgA and IgM   in the serum and broncho-alveolar lavage fluid   (BALF) in those patients, moreover the serum complement C٣   levels and raised levels of IgG, IgA in the serum and BALF persisted by the end of the ٩ months anti TB therapy.١١.

In keeping with our findings , Suzuki and Colleages , in a study about the sequential changes of serum acute phase receding in response to anti- tuberculosis   reported a significant   reduction   in   the   serum immunoglobulin levels after receiving therapy, so as C- reactive   protein   and erythrocyte sedimentation rate (ESR)١٢.

The complement levels and in agreements with our results , Sai Baba et al , reported a significant Increase in the serum levels of complement C٣ in untreated patients with pulmonary   TB in comparison   to treated groups of patients and healthy controls١٣. Furthermore,   Dubaniewcz   and Sztaba – Kanin, reported a significant elevations in complements C٣ levels in active cases of pulmonary TB   in comparison to inactive cases and healthy controls and a tendency towards significant reduction in its level after ٢ months of therapy١٤.

Yildirim   and Colleages, assessed   the complement and immunoglobulin levels in the serum and ascetic fluid in patients with TB ascites in comparison to bacterial peritonitis and malignant   ascites . They reported an increase in the serum IgM , complement C٣ and C٤ with an increase in the IgM , IgA , IgG in the ascitis fluid of patients with TB ascites٧. The elevated in the serum and ascetic fluid of complements C٣ could be attributed to several mechanisms , such as inhibition of serum and ascetic fluid complement –factor consumption and/or   improved   hepatic complement synthesis.١٥,١٦

A recent study by Dubaniewcz and Coworkers in ٢٠٠٤ ,about immunoglobulin parameters in pulmonary TB, reported a significant increase in the serum levels   of IgG, IgA   and   complements C٣, C٤ their patients in comparison to healthy   controls٣. In ٢٠٠٥ a study conducted by Gupta and Colleages , studied the serum level of IgG subclasses in patients with active pulmonary TB. They reported a significant elevation   in IgG١, IgG٣ with moderate raise in IgG٢.١٧

The elevation in the immunoglobulin levels in patients with pulmonary tuberculosis, reported in the present work may be interpreted   as a humoral response to mycobacterial antigens.١٨

In conclusion tuberculosis as a disease and anti-TB therapy do affect the immune system as reflected   by the levels of immunoglobulin (IgG, IgA, IgM) and complements (C٣ , C٤) in comparison to healthy controls.

References

١. Bhatia AS, Kumar S , Harinath BC. Immunodiagnosis of tuberculosis : An update . Indian J Clin Biochem ٢٠٠٣ ,١٨(٢) :١-٥.

٢. Giasuddin ASM , Gad MA , Ziu MM. Humoral immune response in Libyan patients with chronic and acute bacterial infections . J Islamic Acad Sci ١٩٩٠,٣ (٢) : ١٣٩-١٤٢.

٤. Alarcon –Segovia D, Fishbein E. Serum immunoglobulins in pulmonary tuberculosis. Chest ١٩٧١ ; ٦٠: ١٣٣-١٣٦.

٥. Buckly CE, Dorseg MA, A comparison of serum immunoglobulin concentrations in sarcoidosis and tuberculosis . Ann Intern Med ١٩٧٠;٧٢ :٣٧.

٦. Jose P Complement –derived peptide mediators of inflammation . Br Med Bull ١٩٨٧;٤٣: ٣٣٦-٣٤٩.

٧. Yildirim B, Sari R, Sezgin N, Sevinc A, Hilmioglu   F.   Complements   and immunoglobulin levels in serum and ascetic fluid of patients with spontaneous bacterial peritonitis ,malignant ascites and tuberclous peritonitis. South Med J ٢٠٠٢; ٩٥(١٠):١١٥٨-١١٦٢.

٨. Mancini G, Carbonara AO, Heremans JF . Immunochemical quantitation of antigens by   single   radial   immunodiffusion   . Immunochemist ١٩٦٥;٢:٢٣٥-٢٥٤.

٩. Jain VK , Bishnoi HS , Beniwal OP , Misra SN. Immunoglobulin profile in pulmonary tuberculosis. JPGM ١٩٨٤;٣٠(٢):٨٠-٨٤.

١٠.Wong CT, Saha N. Changes in serum proteins (albumin , immunoglobulin and acute phase proteins)   in pulmonary tuberculosis during therapy . T\ubecle ١٩٩٠;١(٣):١٩٣-١٩٧.

١١.Sharma SK, Pande JN, Singh YN, Verma K, Kathait SS, Khara SD , etal. Pulmonary function and immunoglobulin abnormalities in miliary tuberculosis . Am Rev Respir Dis ١٩٩٢;١٤٥ (٥) :١١٦٧-١١٧١.

٣. Dubaniewicz A, Sztaba –Kania M, Hoppe A. Analysis of some immunoglobulin parameters in pulmonary tuberculosis . Pol Merkuriusz Lek ٢٠٠٤;١٦ (٩٢) :١٢٣-١٢٧.

١٢.Suzuki K, Takashima Y, Yamada T, Akiyama J Yagi K, Kawashima M,etal. The sequential changes of serum acute phase reactants in response to anti tuberculosis chemotherapy . Kekkaku ١٩٩٢;٦٧(٤):٣٠٣-٣١١.

١٣.Sai Baba KS, Moudgil KD , Jain RC, Srivastava LM. Complement activation in pulmonary tuberculosis . Tubercle ١٩٩٠; ٧١(٢):١٠٣-١٠٧.

١٤.Dubaniewicz   A, Sztaba –Kania M. Circulating   immune   complex   and complement C٣ in a course of pulmonary tubecolusis . Pol Merkuriusz Lek ٢٠٠٢;١٢ (٧٢):٤٩١-٤٩٥.

١٥. Fromkes JJ , Thomas FB, Mekhjian HS , Evans M. Antimicrobial activity of human ascetic fluid . Gastroenterol ١٩٧٧;٧٣:٦٦٨-٦٧٢.

١٦.Colter HR , Alper CA, Rosen FS . Current concepts in immunology , genetics and biosynthesis of complement proteins . N Eng J Med ١٩٨١;٣٠٤:٦٥٣-٦٥٦.

١٧.Gupta S, Shhende N, Bhatia AS , Kumar S, Harinath BC. IgG subclass antibody response to mycobacterial serine proteins at   different   stages   of   pulmonary tuberculosis. Med Sci Monit ٢٠٠٥;١١(١٢): ٥٨٥-٥٨٨.

١٨..Skvor J, Trkna E, Kugukova Z. Immuno-profile studies in patients with pulmonary tuberculosis. Correlation of levels of different classes of immunoglobulin and specific antibodies with the extent of tuberculosis. Scand J Dis ١٩٧٩;٦٠:١٦٨-١٧١.