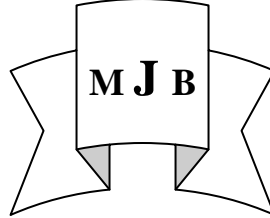


Some Biochemical Changes in Patients with Pulmonary Tuberculosis in Babylon Governorate

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Abstract

This study was designed to investigate the changes of some biochemical parameters in patients with pulmonary tuberculosis in Babylon province. Ninety patients with pulmonary tuberculosis (45 males and 45 females) and 40 healthy controls (20 males and 20 females) included in present study. Patients were classified into 3 groups: group 1 included newly diagnosed patients, group 2 included patients after two months from starting treatment and group 3 included patients after six months from starting treatment. The mean age was 44 ± 2 years for patients and 42 ± 2 years for the control. It has been found that values of C-reactive protein (CRP), calcium and sodium for males zinc for both sexes were insignificantly changed but for CRP, calcium and sodium for females were significantly changed in group 1 in comparison with group 2. Values of zinc for both sexes were insignificantly changed while values of CRP, calcium and sodium for both sexes were significantly changed in group 1 in comparison with group 3. This study showed that values of CRP, calcium, zinc and sodium for both sexes were significantly changed in group 1 in comparison with healthy controls. Values of zinc and potassium for both sexes, calcium and sodium for females were insignificantly changed while values of CRP for both sexes, calcium and sodium for males were significantly changed in group 2 in comparison with group 3. This study showed that values of potassium for both sexes were insignificantly changed while values of CRP, calcium, zinc and sodium for both sexes were significantly changed in group 2 in comparison with healthy controls. The results proved that values of CRP and potassium for both sexes, calcium and sodium for males were insignificantly changed while values of calcium and sodium and for females were significantly changed in group 3 in comparison with healthy controls.

الخلاصة

صممت هذه الدراسة لغرض تقييم بعض التغيرات الكيموحيوية في مرضى التدرن الرئوي في محافظة بابل. أجريت هذه الدراسة في الفترة من تشرين ثاني/٢٠١٠ ولغاية آذار/٢٠١١ في العيادة الاستشارية للأمراض الصدرية والتنفسية في الحلة، وحدة التدرن في قطاع الحلة للرعاية الصحية الأولية و وحدة التدرن في قطاع المسيب للرعاية الصحية الأولية وشملت (٩٠) مريض مصابين بالتدرن الرئوي (٤٥ من الذكور و٤٥ من الإناث) كان متوسط أعمارهم (43.5 ± 1.6 عاماً) و(٤٠) عينة من الناس الاصحاء (٢٠ من الذكور و ٢٠ من الإناث) كان متوسط أعمارهم (41.7 ± 1.9 عاماً). المرضى كانوا على ثلاثة مجاميع ، المجموعة الاولى شملت المرضى الجدد ، المجموعة الثانية شملت المرضى بعد شهرين من العلاج والمجموعة الثالثة شملت المرضى بعد ستة أشهر من العلاج. النتائج: بينت الدراسة أن قيم بروتين (سي) تفاعلي (CRP)، الكالسيوم والصوديوم للذكور والزنك للإناث، أظهرت تغيرات غيرمعنوية، ولكن CRP، الكالسيوم والصوديوم للإناث أظهرت تغيرات معنوية في المجموعة الاولى مقارنة بالمجموعة الثانية من المرضى. قيم الزنك لكلا الجنسين أظهرت تغيرات غيرمعنوية، بينما قيم CRP، الكالسيوم والصوديوم لكلا الجنسين أظهرت تغيرات معنوية في المجموعة الاولى مقارنة بالمجموعة الثالثة. هذه الدراسة وجدت ان قيم CRP، الكالسيوم، الزنك والصوديوم لكلا الجنسين أظهرت تغيرات معنوية في المجموعة الاولى مقارنة بمجموعة السيطرة. قيم الزنك لكلا الجنسين، الكالسيوم والصوديوم للإناث أظهرت تغيرات غيرمعنوية، بينما قيم CRP لكلا الجنسين، الكالسيوم والصوديوم للذكور أظهرت تغيرات معنوية في المجموعة الثانية مقارنة بالمجموعة الثالثة. هذه الدراسة أشارت الى ان قيم CRP، الكالسيوم، الزنك، والصوديوم لكلا الجنسين أظهرت تغيرات معنوية في المجموعة الثانية مقارنة بمجموعة السيطرة. النتائج أشارت الى ان قيم

CRP لكلا الجنسين، الكالسيوم والصوديوم للذكور أظهرت تغيرات غير معنوية، بينما قيم الكالسيوم والصوديوم للإناث أظهرت تغيرات معنوية في المجموعة الثالثة مقارنة بمجموعة السيطرة.

Introduction

Tuberculosis is the world's second most common cause of death from infectious disease, after acquired immune deficiency syndrome [1].

It is a disease associated with poverty, overcrowding, debilitating diseases, drug abuse, alcoholism, homelessness and immunodeficiency and it has become more important with the advent of the HIV epidemic, presenting in less familiar ways and following a more aggressive and persistent course [2].

Tuberculosis (TB) caused by infection with *Mycobacterium tuberculosis*, which is part of a complex of organisms including *Mycobacterium bovis* (reservoir cattle) and *Mycobacterium africanum* (reservoir human) [3].

The increasing incidence of tuberculosis (TB) is a major concern to public health policy-makers in both developing and developed countries, approximately one-third of the world's population is infected with *Mycobacterium tuberculosis*, and three million people die every year (342 death / hour) due to TB [4]. Accurate and rapid diagnosis is the key to controlling the disease but, the current routine diagnostic tests for TB (chest x-ray, culture, tuberculin skin test and acid-fast staining) all have their limitations, in which chest x-ray alone is inconclusive, culture takes too long to produce a result, the tuberculin skin test lacks specificity and reliability, serological tests using different TB antigens to detect *Mycobacterium tuberculosis* infection are fast but lack the desired sensitivity [5].

The primary method for diagnosing pulmonary tuberculosis in low-income and middle-income countries is direct

sputum smear microscopy, which is fast, inexpensive, and specific for *Mycobacterium tuberculosis* but, it has low sensitivity because of variable quality of the test in program conditions [6].

New method of diagnosis, such as nucleic acid amplification technology which although specific, can yield false-positive results, as well as immunologic tests which have their disadvantages and unanswered questions, so we still need accurate and rapid method of diagnosing both active and latent TB infection [5]. In pulmonary tuberculosis many hematological and biochemical abnormalities are common and they are valuable aids to diagnosis [7].

CRP can help to distinguish between pulmonary TB and some common types of bacterial pneumonia. Therefore, CRP might have a role in the diagnostic algorithm as rapid, noninvasive tests [8]. Hypercalcemia is known to occur in granulomatous diseases, it is a well recognized complication of active tuberculosis but, the reported incidence of hypercalcemia in TB varies widely between countries, probably because of variations in the Vitamin D and calcium intake and the amount of sun exposure [9]. The nutritional status of patients with active pulmonary TB is poor including low serum zinc [10]. Several studies have demonstrated that the serum levels of zinc decrease significantly during active tuberculosis and increase following recovery after institution of ant tubercular therapy [11].

Although there have been previous reports on hyponatremia in patients with tuberculosis, we are reporting an interesting cases of tuberculosis in whom

the initial presenting manifestation was lethargy due to hyponatremia probably resulting from Syndrome of inappropriate antidiuretic hormone secretion (SIADH) [12]. The SIADH was originally described in 1975 in patients with bronchogenic carcinoma. SIADH is the most common cause of normovolemic hyponatremia, which occurs due to non-physiologic antidiuretic hormone release from the posterior pituitary or an ectopic source such as carcinoma of the bronchi, stomach, prostate Etc. [13].

Aim of the study

This study is aimed to estimate some biochemical changes in patients who are infected with pulmonary tuberculosis in Babylon province to help the medical staff in the early and precise detection and follow up of this disease. This study is designed to determine the following:

1. Measurement serum C-reactive protein.
2. Serum calcium.
3. Serum zinc.
4. Serum sodium.

Materials and Methods

This study was carried out for the period starting from November / 2010 to March / 2011. Ninety patients with pulmonary tuberculosis (45 males and 45 females) were assessed by specialist doctor on the basis of history, clinical examination, chest radiography and, direct smear sputum examination and 40 healthy controls (20 males and 20 females). The patients are classified into 3 groups and each group composes of 30 patients (15 male and 15 female). Group 1 included newly diagnosed patients before starting treatment, group 2 included patients after two months from starting treatment and group 3 included patients after six months from starting

treatment (at the end of treatment). Those patients were the attendants to the Al-Hilla Consultation Clinic for Chest and Pulmonary Diseases, Al-Hilla Primary Health Care District (TB Unit) and Al-Musayyib Primary Health Care District (TB Unit). Because many conditions may interfere with the results of measured parameters and the outcome of the study, we excluded from the study subjects with the following conditions

1. Extra pulmonary tuberculosis.
2. Non-tuberculous pulmonary infections.
3. Chronic pulmonary disease.
4. Chronic liver disease
5. Chronic renal disease.
6. Diabetes mellitus.
7. Smoking.
8. Pregnancy.
9. Chronic cardiovascular diseases.

The collection of blood was done in Al-Hilla Consultant Clinic for Chest And Pulmonary Diseases, Al-Hilla Primary Health Care District (TB Unit) and, Al-Musayyib Primary Health Care District (TB Unit) from 8.30 A.M. to 11.30 A.M. Five ml. of blood were drawn for each biochemical study in plain tubes without anti-coagulant, to be used for preparing sera. Each sample was labeled and given a serial number together with the patient name. The serum samples were frozen at -20°C for biochemical analysis [14].

The qualitative and semi-quantitative methods are used for determination of CRP according to the procedure recommended by the CRP Latex kit from Spinreact, Spain. The assay is performed by testing a suspension of latex particles coated with anti-human CRP antibodies against unknown serum. The presence of visible agglutination indicates an increase in levels of CRP to a clinically significant level (according to procedure

recommended by CRP Latex kit from Spinreact, Spain) [15].

Calcium in the sample reacts with O-cresolphthaleine at alkaline pH. The colored complex formed is proportional to the amount of calcium present in the sample. The intensity of the color was measured photometrically by using spectrophotometer at 570 nm wave length (according to procedure recommended by the serum calcium from Human company, Germany) [15].

Serum zinc reacts with chromogen present in the reagent forming a colored compound, which color intensity that is proportional to the zinc concentration present in the sample by using spectrophotometer at 578 nm and the color is stable for 20-30 minutes (Zinc kit L.T.A Italy) [16].

Flame Photometry was used for the quantitative measurement of sodium in the body fluids. The principle is when atoms of many metallic elements, given sufficient energy such as that supplied by a hot flame, emit this energy at wavelengths characteristic for the element. A specific amount or quantum of thermal energy is absorbed by an orbital electron. The electrons, being unstable in this high energy (excited) state, release their excess energy as photons of a particular wavelength as they change from the excited to their previous or ground state. If the energy is dissipated as light, the light may consist of one or more than one energy level and therefore of different wavelengths. These line spectra are characteristic for each element. The wavelength to be used for the measurement of an element depends on the selection of a line of sufficient intensity to provide adequate sensitivity as well as freedom from other interfering lines at or near the selected wavelength. Sodium produces a yellow color. This

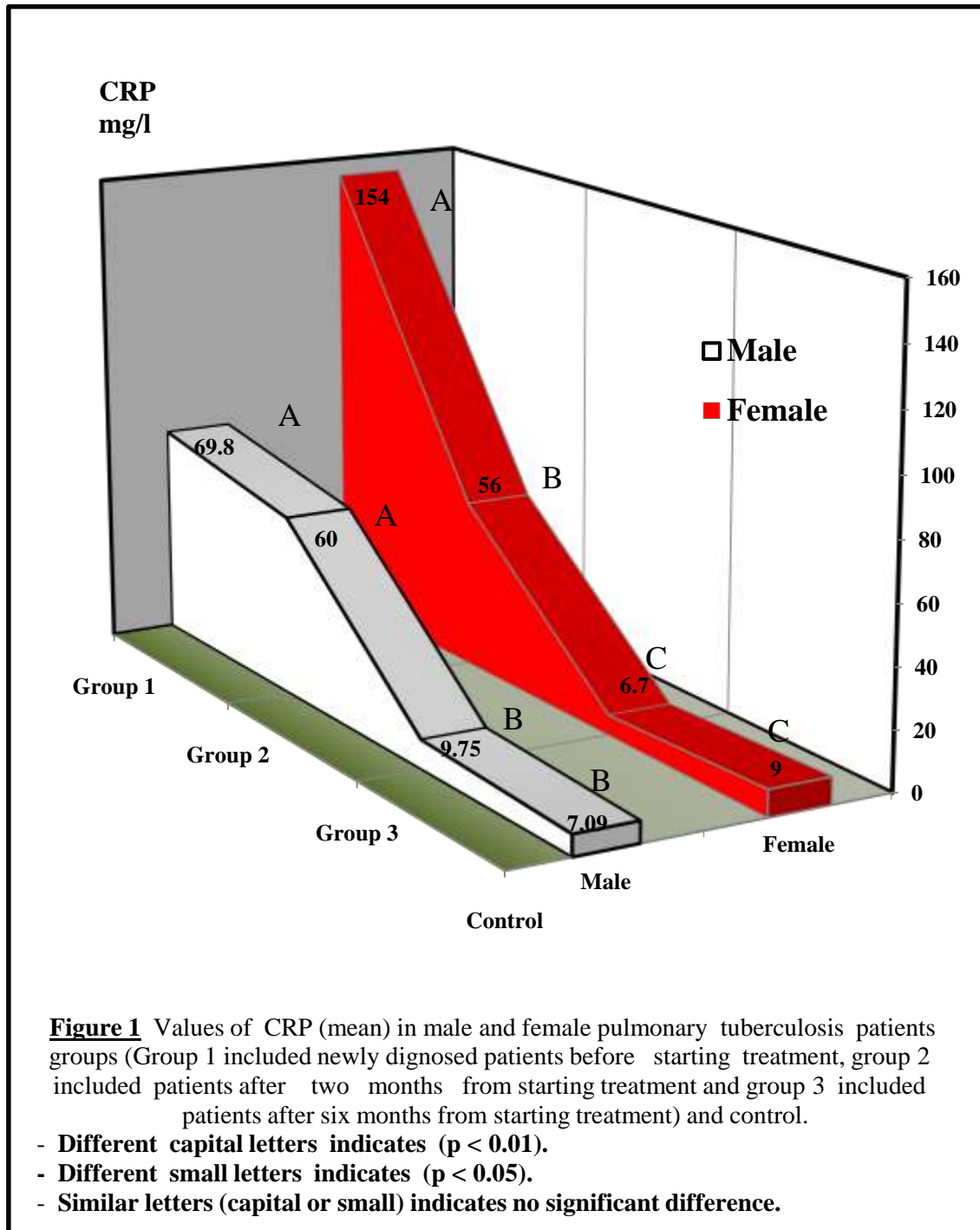
color is characteristic of the metal atoms that are present as cations in solution. Under constant and controlled conditions, the light intensity of the characteristic wavelength produced by the atoms is directly proportional to the number of atoms that are emitting energy, which in turn is directly proportional to the concentration of the substance of interest in the sample according to procedure recommended by the sodium kit from Human company, Germany) [15].

All values were expressed as mean \pm SE. The data were analyzed by using of computer SPSS statistics 11 program. The differences were considered significant when the probability (P) was less than 0.05 ($P < 0.05$) and highly significant when the probability (P) was less than 0.01 ($P < 0.01$). ANOVA test was used to examine the differences between different groups [17].

Results

1. Serum C-reactive protein

The values of total serum C-reactive protein for all the patient groups (1, 2 and 3) of male pulmonary tuberculosis patients are: 69.8 ± 7.568 ; 60 ± 12 and 9.75 ± 1.02 mg/l respectively, and for females are: 154 ± 23.523 ; 56 ± 8 and 6.7 ± 0.667 mg/l respectively. Group 1 values for males are insignificant ($p > 0.05$) while for females they are highly significantly increased ($p < 0.01$) in comparison with group 2. Group 1 values of both males and females are highly significantly increased ($p < 0.01$) in comparison with group 3 and healthy controls. Group 2 values for both males and females are highly significantly increased ($p < 0.01$) in comparison with group 3 and healthy controls. Group 3 values for both males and females are insignificant ($p > 0.05$) in comparison with healthy controls.



2. Serum calcium

Group 1 values for males are insignificant ($p > 0.05$) while for females they are highly significantly increased ($p < 0.01$) in comparison with group 2. Group 1 values for both males and females are highly significantly increased

($p < 0.01$) in comparison with group 3 and healthy controls. Group 2 values for males are highly significantly increased ($p < 0.01$) while for females they are insignificant ($p > 0.05$) in comparison with group 3. Group 2 values for both males and females are highly

significantly increased ($p < 0.01$) in comparison with healthy controls. Group 3 values for males are insignificant ($p > 0.05$) while for females they are highly significantly decreased ($p < 0.01$) in comparison with healthy controls.

3. Serum zinc

Group 1 values for both males and females are insignificant ($p > 0.05$) in comparison with group 2 and group 3. Group 1 values for both males and females are highly significantly decreased ($p < 0.01$) in comparison with healthy controls. Group 2 values for both males and females are insignificant ($p > 0.05$) in comparison with group 3. Group 2 values for both males and females are highly significantly decreased ($p < 0.01$) in comparison with healthy controls. Group 3 values for males and females are highly significantly decreased ($p < 0.01$) in comparison with healthy controls.

4. Serum sodium

Group 1 values for males are insignificant ($p > 0.05$) while for females they are highly significantly decreased ($p < 0.01$) in comparison with group 2. Group 1 values for both males and females are highly significantly decreased ($p < 0.01$) in comparison with group 3 and healthy controls. Group 2 values for males are highly significantly decreased ($p > 0.01$) while for females they are insignificant ($p > 0.05$) in comparison with group 3. Group 2 values for both males and females are highly significantly decreased ($p > 0.01$) in comparison with healthy controls. Group 3 values for males are insignificant ($p > 0.05$) while for females they are highly significantly decreased ($p < 0.01$) in comparison with healthy controls.

Table 1 The changes in serum calcium, serum zinc and serum sodium for pulmonary tuberculosis patients groups (Group 1 included newly diagnosed patients before starting treatment, group 2 included patients after two months from starting treatment and group 3 included patients after six months from starting treatment) and controls.

	Sex	Group 1	Group 2	Group 3	Control
Serum Calcium (mmol/l)		A	A	B	B
	M	2.780 ± 0.030	2.680 ± 0.072	2.380 ± 0.042	2.280 ± 0.093
		A	B	B	C
	F	2.870 ± 0.056	2.550 ± 0.020	2.480 ± 0.040	2.260 ± 0.030
Serum Zinc (µmol/l)		A	A	A	B
	M	10.500 ± 0.324	10.900 ± 0.584	11.500 ± 0.118	16.400 ± 0.337
		A	A	A	B
	F	10.100 ± 0.596	10.300 ± 0.134	11.000 ± 0.191	13.200 ± 0.551
Serum Sodium (mEq/l)		A	A	B	B
	M	126.000 ± 1.898	129.000 ± 0.633	139.000 ± 1.651	141.000 ± 0.919
		A	B	B	C
	F	130.000 ± 0.782	142.000 ± 0.759	142.000 ± 0.623	146.000 ± 0.211

- Values are mean ± SE.
- Different capital letters indicates ($p < 0.01$).
- Different small letters indicates ($p < 0.05$).
- Similar letters (capital small) indicates no significant difference.

Discussion

1.C-reactive protein

In this study results refers that there was a highly significant ($p < 0.01$) increase in CRP levels for both males and females newly diagnosed pulmonary tuberculosis patients (group 1) in comparison with patients at the end of treatment course (group 3) and healthy controls as shown in figure (4.3). These results are convenient with results of a study in Portugal doen by Póvoa [18] which states: after the diagnosis of infection and the start of therapy, serial determinations of CRP provide important information, after the initiation of therapy, a CRP level that remains persistently elevated or continues to rise suggests either a wrong diagnosis or ineffective or inappropriate treatment, on the other hand, a fall in CRP indicates that the infection is resolving.

Also another study supports the findings of this study by Sukhesh and Vidya [19] who said: serum CRP levels may have a role in identifying the advanced and extensive disease patients thereby indirectly helping the health workers to pick up delayed convertors and defaulters, so as to guide them to put in extra efforts on these groups, in tuberculosis control programs.

The disease-induced chronic production of cytokines such as interleukin-6 and tumor necrosis factor- α may induce elevation of body temperature, wasting and hepatic synthesis of acute phase reactant proteins like CRP [20].

2.Serum calcium

In this work, the serum calcium levels for both males and females of pulmonary tuberculosis patients shows a highly significant increase ($p < 0.01$) compared with the control group as in table 4.4. These results are in agreement with the

results of a study done in Abuja, Nigeria in 2006 by Dosumu and Momoh [21] which states that hypercalcemia is common among Nigerian patients with newly diagnosed TB.

On the other hand another studies said: calcium abnormalities especially hypocalcaemia is quite common in patients with pulmonary TB [22, 23].

Playford *et al.* [24] explains these changes declaring that the abnormalities of calcium metabolism are due to deregulated production of 1,25 (OH) $_2$ D $_3$ (calcitriol) by activated macrophages trapped in pulmonary alveoli and granulomatous inflammations.

The obvious disagreement between the above studies is probably due to that: the amount of sun exposure and the circulating levels of 25(OH)D $_3$, a product of hydroxylation of vitamin D $_3$ in the liver, may partly explain the rare occurrence of hypercalcemia in TB patients in countries with temperate climates, this may also possibly explain why hypercalcemia is rare in TB patients in the United Kingdom who have high calcium intake but low vitamin D levels. It has been reported that in tropical climates, where sunlight is abundant, a relatively high level of serum 25(OH)D $_3$ may give rise to hypercalcemia in patients with TB [21].

3.Serum zinc

Zinc deficiency affects host defense in a variety of ways. It results in decreased phagocytosis and leads to a reduced number of circulating T- cells and reduced tuberculin (purified protein derivative) reactivity, at least in animals [10].

The present study observed that, levels of serum zinc for both males and females in newly diagnosed pulmonary tuberculosis patients were significantly decreased ($p < 0.01$) in comparison with

the control group as shown in table 4.4, this results are in agreement with Qureshi *et al.* [25] which states that, there was a statistically significant fall in serum zinc levels in patients with pulmonary TB, and also in agreement with Karyadi *et al.* [10] which says that, the occurrence of low concentrations of plasma zinc was significantly higher in active pulmonary tuberculosis patients than in controls.

According to this study, group 1 values for both males and females are insignificant ($p > 0.05$) in comparison with group 2 and group 3. Group 2 values for both males and females are insignificant ($p > 0.05$) in comparison with group 3 (table 4.4), so serum zinc cannot be used in the follow up of pulmonary TB patients under treatment, this is not convenient with the findings of Qureshi *et al.* [25] which states that, levels of serum zinc improved after institution of ant tuberculosis therapy pulmonary TB patients, and also Ghulam's [11] who said that, estimation of serum zinc levels during the course of tuberculosis could be used as a valuable tool for clinicians to assess response to therapy or effectiveness of the ongoing ant tuberculosis therapy.

These alterations in serum zinc levels in pulmonary tuberculosis patients may be due to redistribution of zinc from plasma to other tissues or reduction of the hepatic production of the zinc-carrier protein α_2 -macroglobulin and to a rise in the production of metallothionein (protein that transports zinc to the liver), and also to the high production of TNF and IL-1ra [26, 20].

4.Serum sodium

Hyponatremia is a common biochemical abnormality in pulmonary tuberculosis in which the syndrome of inappropriate ant diuretic hormone

secretion (SIADH) is one of several causes of hyponatremia. The mechanism of SIADH associated with pulmonary tuberculosis is, however, poorly understood, but as we said ectopic ant diuretic hormone production probably is the case of this abnormality [27].

In this effort serum sodium levels for both males and females of pulmonary tuberculosis patients shows a highly significant decrease ($p < 0.01$) compared with the control group as revealed in table 4.4. The results obtained from the present study are on the same wave length of the results obtained from a study doen in Nigeria by Emokpae [23] in which both of them observed hyponatremia in pulmonary tuberculosis patients while Folaranmi and Adesiyan [28] found that there is no significant difference in the mean value of serum sodium in pulmonary tuberculosis patients in comparison with controls.

Conclusions

Some biochemical abnormalities is quite common in patients with pulmonary TB and physicians must maintain a high index of suspicion for diagnosis of pulmonary TB in patients with these abnormalities. As well as, these parameters can be used as indicators in the assessment of response to chemotherapy.

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