

## Hematological Abnormalities in Saudis Suffering from Pulmonary Tuberculosis and Their Reponce to the Treatment

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**Abstract:** Pulmonary Tuberculosis (PTB) is a common disease in developing countries and efforts have been made to diagnose patients presenting complex hematological and biochemical picture. Hematological abnormalities have been associated with tuberculosis and response to drug therapy often showed varied resistance. However, changes in response to therapy have not fully been determined in PTB patients living in the developing countries. In PTB patients rise in hemogloin and hematocrit levels are used as markers reflecting response to treatment. Furthermore, decrease in platelet count and in white cell count and reduction in Erythrocyte Sedimentation Rate (ESR) were regarded as good indicators to obverve drug response and disease control. During current study mild anemia was frequently observed in PTB patients. Several reports suggested leucocytosis with neutrophilia. Platelet count and erythrocyte sedimentation rate were elevated in PTB which is well influenced and corrected by using different combinations of antituberculosis drugs. Although several investigations have been done on adult male and female PTB parients in Saudi Arabia, however, there is no comprehenssive report available on the significance of different haematological parameters in pretreatment and post-treatment PTB patients. Current study was designed to investigate hematological changes both in adult male and female Saudi PTB patients. All the parameters at the time of diagnosis and 6 weeks post-treatment were studied and the results are present in current communication.

**Key words:** Pulmonary tuberculosis, Saudi adult male and female patients, hematological parameter, pre-treatment values, post-treatment results

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### INTRODUCTION

Pulmonary Tuberculosis (PTB) is still a common disease in developing countries (WHO, 2000; Espinal *et al.*, 2001) and a global trend in the resistance to antituberculosis drugs was observed (Arends, 1950; Bukhari and Alrajhi, 2007; Daves *et al.*, 2009). The comprehenssive investigations on hematological changes and abnormalities associated to tuberculosis are still lacking (Cartwright, 1966; Singh *et al.*, 2001). Hemorheological changes in response to therapy have also not been fully determined in PTB patients living in developing countries (Awodu *et al.*, 2007).

In Saudi Arabia, the data from different reginal hospitals located in five provinces was collected to know the prevalence, clinical features and results of therapy of tuberculosis, in patients on dialysis. The prevalence of TB was found higher in Saudi Arabia. Among the patients, the main causes of death was found to be due to sepsis, cardiovalscular and sudden death (Hassan *et al.*, 2003). The susceptibility of *Mycobacterium tuberculosis* in the Eastern Province of Saudi Arabia to one or the other anti-tubercular drug, was investigated by several

researchers Al-Jama *et al.* (1999), Schwoebel *et al.* (2000), Alrajhi and Al-Barrak (2002), Al-Rubaish *et al.* (2001), Kordy *et al.* (2004), Al-Tawfiq *et al.* (2005), Alrajhi and Tawfiq (2006) and Bukhari *et al.* (2007). Previous treatment was found to be a common risk factor for extensively drug resistant and multidrug-resistant in tuberculosis (Schwoebel *et al.*, 2000; Singla *et al.*, 2003a; Kliiman and Altraia, 2009a, b).

The diagnosis of tuberculosis mainly relies on acid-fast bacilli smear and culture results (Gladwion and Trattler, 2007). However, nucleic acid amplification test and PCR test were also found reliable (Ben-Kahla *et al.*, 2009; Laraque *et al.*, 2009). The delay of diagnosis in some cases, was attributed to the PTB (one of the complications of hypercortisolism), because the PTB was presented in the form of multiple nodules throught the lungs (Jang *et al.*, 2009).

Hematological abnormalities have been associated with tuberculosis (Singh *et al.*, 2001; Al-Omar and Oluboyede, 2002; Awodu *et al.*, 2007). In active PTB, anemia and iron deficiency erythropoiesis was observed. There was a close corelation between acid-fast bacilli in sputum and abnormal hematological values

(Morris *et al.*, 1989; Singla *et al.*, 2003b). During treatment improvements in some of the hematological values such as, rise in hemoglobin and hematocrit levels, were used as markers reflecting response to treatment (Singla *et al.*, 2003a; Alrajhi and Tawfiq, 2006). Furthermore, decrease in platelet count and in white cell count and reduction in Erythrocyte Sedimentation Rate (ESR) were regarded as good indications of disease control (Morris *et al.*, 1989). In Saudi Arabia, there is no systematic documentation about pre-treatment and post-treatment changes in hematological parameters of patients suffering from PTB.

In the current study, an attempt has been made to investigate hematological changes in both adult male patients and female patients suffering from PTB. All the parameters at the time of diagnosis and 6 weeks after treatment were collected and the results are present in the present communication.

## MATERIALS AND METHODS

In the current study, a total of fifty proven pulmonary tuberculosis patients (30 males and 20 female Saudis) were included. Age of the male patients ranged between 22-70 years with a means of 42 years; while the age of the females ranged between 23-65 years with a mean of 38 years. Among the male patients 95% patients were unemployed and 5% were working. Among female patients all were house-wives with the exception of 2% patients who were students. All patients were positive with *Tubercle bacilli* in sputum (ZN stain).

**Treatment:** All patients were on 3 drugs treatment namely: Streptomycin, Rifampicin and Isoniazid and were hospitalized for 6 weeks or more.

**Instruments, reagents and kits:** For the analysis of blood samples following instruments were used: Coulter counter-STK-S (USA); BM/Hitachi 717 Automatic analyzer (Boehringer Mannheim); Cobas Mira Plus analyzer (Roche, UK).

Blood samples were collected from all male and females properly diagnosed patients suffering from pulmonary T.B and had acid-fast bacilli in the sputum. Venous blood about 10 mL was collected from each patient where, 3 mL of the blood was transferred to Ethylene Diamine Tetra Acetic Acid (EDTA) tube; 4 mL blood was transferred to a clean screw-capped glass tube without having any anti-coagulant. The samples were put under standard laboratory temperature and processed to obtain serum by using centrifuge. However, for

measuring Erythrocyte Sedimentation Rate (ESR) 3 mL of citrate solution was added. The analysis was performed in the Central Laboratory, King Saud Medical Complex, Ministry of Health, Riyadh, Saudi Arabia. All tests were performed following standard laboratory protocols.

## RESULTS

The mean, median, standard deviation and range values for different hematological parameters for the patients suffering from Pulmonary Tuberculosis (PTB) at the time of diagnosis and at the end of the treatment were recorded.

The skewness values demonstrated that the distribution of Hemoglobin (Hb) concentration, hematocrit ratio and Red Blood Cell count (RBC) were negatively skewed towards the lower values. The red cell indices values including the mean values for Mean Cell Volume (MCV), Mean Cell Hemoglobin (MCH) and Mean Cell Hemoglobin Concentration (MCHC) for all 50 patients at diagnosis (starting point) are shown in Table 1.

The total White Blood Cell (WBC) and differential counts in Saudi Pulmonary Tuberculosis (PTB) patients at diagnosis were also investigated. The mean, median, standard deviation, range values obtained for the total and differential white blood cell counts in patients are depicted in Table 2.

The frequency distribution of the values skewed positively towards higher values except neutrophils. The significantly higher ( $p < 0.01$ ) White Blood Cells (WBC) and neutrophils demonstrated leucocytosis in patients before treatment.

As regards platelets count of the Saudi PTB patients included in the current study is concerned, the mean, median, standard deviation and range values obtained are given in tabular form (Table 3). A highly significant ( $p < 0.001$ ) increase in platelet count was noticed in Saudi PTB patients as compared with the normal Saudi persons.

The Erythrocyte Sedimentation Rate (ESR) for both male and female Saudi PTB patients was measured and the ESR data is shown in Table 4. Both in untreated male and female PTB patients the ESR values were significantly higher as compared to normal control values.

Treatment with anti-tuberculosis drugs (Streptomycin, Isoniazid and Rifampicin) showed significant improvement in Hb, PCV, RBC, MCV, MCH and MCHC values and the results are shown in Table 5. Post-treatment levels of hemoglobin and hematocrit were found to be significantly ( $p < 0.001$ ) higher as compared to the pre-treatment values of PTB patients.

Table 1: Hematological parameters including Hb, PCV, RBC, MCV, MCH and MCHC in male and female Saudi patients suffering from pulmonary tuberculosis at diagnosis (the starting point)

Parameters	Male patients (N = 30)				Female patients (N = 20)			
	Mean	Median	SD	Range	Mean	Median	SD	Range
Hb (g dL <sup>-1</sup> )	12.68	12.10	2.25	6.8-15.4	11.54	11.60	1.78	8.0-14.7
PVC (%)	37.44	37.30	6.86	20.4-47.1	36.87	37.46	3.69	30.9-43.50
RBC ( $\times 10^{12}/L$ )	4.61	4.74	0.74	2.6-6.2	4.76	4.76	0.36	4.10-5.43
MCV (fL)	83.28	82.40	7.28	59.6-90.4	77.46	79.75	5.70	64.2-85.0
MCH (Pg)	28.07	27.25	2.76	19.2-30.6	25.15	25.75	2.18	20.4-28.5
MCHC (g dL <sup>-1</sup> )	32.86	32.90	0.75	30.8-34.6	32.43	32.40	1.03	30.8-34.3

Table 2: Values of total and differential of White Blood Cells count (WBC) in all male and female Saudi patients suffering from Pulmonary Tuberculosis (PTB) at diagnosis

Parameters ( $\times 10^9/L$ )	Male patients (N = 30)				Female patients (N = 20)			
	Mean	Median	SD	Range	Mean	Median	SD	Range
WBC total	10.32	10.50	3.63	3.4-19.1	8.88	9.35	3.23	4.10-17.20
Neutrophil	6.24	6.50	17.73	1.2-9.1	5.97	6.20	10.44	4.0-7.3
Lymphocyte	2.12	2.50	5.53	0.6-4.1	2.35	2.35	8.69	1.0-4.2
Monocyte	0.93	0.95	8.22	0.2-4.5	1.17	0.90	6.9	2.0-3.0
Eosinophil	0.41	2.50	5.53	0.0-2.5	0.42	0.30	3.66	0.1-1.6
Basophil	0.10	1.0	1.77	0.0-0.9	0.07	0.05	0.86	0.0-3.0

Table 3: Values of platelet count in fifty male and female Saudi patients suffering from pulmonary tuberculosis at diagnosis point

Parameters	Male patients (N = 30)				Female patients (N = 20)			
	Mean	Median	SD	Range	Mean	Median	SD	Range
Platelets ( $\times 10^9/L$ )	374.13	366	123.26	11-601	385.85	400.50	111.14	168-557

Table 4: Erythrocyte Sedimentation Rate (ESR) in adult male and female Saudi PTB patients at diagnosis

Parameters	Male patients (N = 30)				Female patients (N = 20)			
	Mean	Median	SD	Range	Mean	Median	SD	Range
ESR (mm h <sup>-1</sup> )	70.13	73.50	34.89	1-140	73.65	77.5	28.43	6-113

Table 5: Hematological parameters including Hb, PCV, RBC, MCV, MCH and MCHC in male and female Saudi PTB patients after 6 weeks of treatment

Parameters	Male patients (N = 30)				Female patients (N = 20)			
	Mean	Median	SD	Range	Mean	Median	SD	Range
Hb (g dL <sup>-1</sup> )	14.55	14.60	2.24	8.9-17.80	13.69	13.85	1.46	10.4-15.60
PVC (%)	48.37	48.15	12.13	28.8-62.60	44.01	43.55	6.72	31.3-55.90
RBC ( $\times 10^{12}/L$ )	5.36	5.36	0.57	4.12-6.27	5.15	5.17	0.38	4.58-5.90
MCV (fL)	89.94	89.90	12.51	55.2-112.7	85.21	83.20	10.90	66.7-109.2
MCH (Pg)	27.17	28.10	2.98	17.0-30.6	26.58	26.90	2.54	21.10-32.0
MCHC (g dL <sup>-1</sup> )	30.45	29.90	3.07	26.2-35.7	31.48	32.80	3.34	25.3-34.90

## DISCUSSION

The values of hemoglobin, hematocrit ratio and red cell indices obtained for male and female patients at diagnosis of PTB and after 6 weeks of treatment with Staptomycin, Isoniazid and Refampacin are presented in Table 1-5.

At diagnosis the mean hemoglobin concentrations were 12.58 g dL<sup>-1</sup> for males and 11.54 g dL<sup>-1</sup> for the female patients. Both the values were significantly lower than the mean values for healthy male and female Saudis 15.2 and 12.9 g dL<sup>-1</sup>, respectively.

The hematocrit values of the same patients at diagnosis (male 37.44%, female 36.87%), were found lower than the values obtained for healthy Saudis (male 45%, female 38%). However, literature review showed that the mean hematocrit in Nigerian untreated PTB patients were

much lower than the values found in the current study (Akintunde *et al.*, 1995). During the present study, a mild anemia was observed in 18 out of 30 male PTB patients (60%) and 9 out of 20 female patients (45%). The observations are in agreement with the earlier reports demonstrating mild anemia to be a common feature in PTB patients (Morris, 1989; Morris *et al.*, 1989; Ebrahim *et al.*, 1995; Lee *et al.*, 2006; Miah *et al.*, 2007). The precise mechanism of anemia in PTB is not clearly known, however, anemia due to inflammation as well as that of iron deficiency has been implicated (Douglas and Adamson, 1975; Das *et al.*, 2003). The subnormal hemoglobin and hematocrit levels occurring in Saudi PTB patients, might at-least partially be associated to the underlying chronic inflammatory disorder (Lee, 1983; Baynes *et al.*, 1986, 1987; Morris *et al.*, 1989; Lee *et al.*, 2006).

Factors such as decrease in red cell survival and reduced erythropoietin response by the bone marrow erythroid cells are also known to cause anemia (Erslev *et al.*, 1980; Lee, 1983). However, in active PTB, there was no evidence to suggest that anemia in patients was secondary to iron-deficient erythropoiesis (Baynes *et al.*, 1986). The findings were further supported by an earlier study, where 60% of the PTB patients were found suffering from iron deficiency anemia (Bainton and Finch, 1964; Oluboyede and Onadeko, 1978). The other possible cause of observed anemia in PTB patients might also be associated to inflammatory process causing anemia due to cytokines production (Ebrahim *et al.*, 1995).

In the current study, the Mean Cell Volume (MCV), Mean Cell Hemoglobin (MCH) and Mean Cell Hemoglobin Concentration (MCHC) of all the patients were measured before treatment (Table 1). The MCV in males was significantly higher ( $p < 0.001$ ) as compared to the healthy matched persons. However, in the females patients the values obtained were statistically non-significant. Both, in male and female PTB patients, the MCHC values were almost similar. The red cell indices for the healthy adult Saudi males were 86 fL, 29 pg and 33%, while for females 84 fL, 28.3 pg and 33%. The RBC indices in the untreated male PTB patients showed lower values as compared to normal Saudi males. The MCV in male patients (83.28 fL) was also lower than in the normal males (86 fL).

As regards the MCH in male PTB patients in the current study is concerned, it was significantly lower as compared to normal males. Furthermore, MCHC values were lower in PTB patients as compared to the control but the difference was statistically not significant. In Saudi female PTB patients RBC indices showed MCV as well as MCHC values to be significantly ( $p < 0.05$ ) lower as compared to the normal control values and the values obtained in earlier studies (Baynes *et al.*, 1986; Morris *et al.*, 1989). After anti-tuberculosis treatment with Streptomycin, Rifampicillin and Isoniazid, the RBC indices were affected both in male and female PTB patients and MCV, MCH and MCHC values reached closer to the normal values. These changes might be included in the follow up procedure in PTB patients.

Generally, anemia in chronic diseases is of normocytic normochromatic type, although in a few cases, microcytosis and hypochromia also occurred. In the current study, anemia occurred in 60% male PTB patients and 45% female patients. The blood cell morphology showed normocytic normochromia in 80% of the patients, while only 20% PTB patients had microcytic and hypochromic RBC. Such patients had correspondingly lower MCV and MCH values. The findings are supported by a previous reports, where no evidence of iron

deficiency erythropoiesis was found and MCV values were not reduced. In the present study, RBC morphology in PTB patients was found to be mainly of normocytic normochromic type and during medication, the blood film showed normochromic picture as evidenced in 95% patients earlier (Baynes *et al.*, 1986; Lombard and Mansvelt, 1993; Dosumu, 2001).

It is worth mentioning that Morris *et al.* (1989) also recorded anemia to be a common feature in PTB patients and the majority patients had normocytic normochromic red cell indices (Bessman *et al.*, 1983; Lee, 1983). In another earlier report, anemia occurred in 72% of patients (Lombard and Mansvelt, 1993) where RBC morphology was predominantly normocytic normochromic in the anemic patients. Anemia was also found in 70% males and 63% females PTB patients and among all PTB patients, 95% were having normocytic normochromic RBCs (Baynes *et al.*, 1986; Monzan *et al.*, 1987; Morris, 1989; Morris *et al.*, 1989; Lombard and Mansvelt, 1993). Anemia was also reported in 93.6% Nigerian PTB patients (Olaniyi and Aken'Ova, 2003a). Based on the results of the current study and earlier reports, it may be concluded that patients suffering from PTB have RBC morphology of normocytic normochromatic type and possess mildly reduced hemoglobin concentration, hematocrit, PCV values and RBC indices. However, MCHC remain within the normal range. These findings further demonstrated that anemia and RBC morphology noticed were similar to anemia of chronic disorders (Lee, 1983; Lee *et al.*, 2006).

As regards the total White Blood Cells (WBC) count is concerned, it was significantly higher ( $p < 0.01$ ) before treatment in as compared to the normal control values (Al-Buhairan, 1998; Singh *et al.*, 2001; Olaniyi and Aken'Ova, 2003b; Awodu *et al.*, 2007) indicating leucocytosis in Saudi patients suffering from PTB. The abnormal hematological results obtained in the current study are in full agreement with the earlier studies where marked leucocytosis was prevalent in male PTB patients and relatively lesser in female patients (Stenius-Aarniala and Tukianen, 1979; Hunt *et al.*, 1987; Morris, 1989; Lombard and Mansvelt, 1993; Bose *et al.*, 1995). Neutrophil composition of male and female PTB patients was found higher as compared to the normal healthy Saudis. However, the neutrophil count was relatively higher in the female patients as compared to the male PTB patients. The findings are in agreement with the earlier reports (Lombard and Mansvelt, 1993). Hence, it could be concluded that leucocytosis due to neutrophils is associated with PTB.

During current study there were no statistically significant increase in lymphocyte count in PTB patients at the time of diagnosis. There were some

conflicting reports on lymphocytosis and lymphopenia (Onwubalili *et al.*, 1983; Onwubalili, 1990; Akintunde *et al.*, 1995). However, the findings are supported by a report where lymphocytic reaction in the pulmonary tissue was reported to be high in tuberculosis along with lung tissue decay, nonspecific inflammation and magnitude of neutrophilic reaction (Lobacheva and Evgushchenko, 1998). In addition, in the sputum of patients with interstitial lung disease, generally, the percentage of neutrophils was also found higher (Sobiecka *et al.*, 2008).

In patients suffering from PTB monocytosis was also observed in the present investigation. Some earlier reports suggested monocytosis to occur only in a small number of patients, while monocytopenia occurred in about 50% of their patients (Morris *et al.*, 1989; Lombard and Mansvelt, 1993). The results of the present study on Saudi PTB patients are contrary to the earlier findings on lymphocytosis or lymphopenia (Onwubalili *et al.*, 1983; Morris *et al.*, 1989; Onwubalili, 1990; Akintunde *et al.*, 1995).

In the present study, platelet counts were found higher both in male and female untreated PTB patients as compared with the normal values for Saudi population. However, thrombocytosis was significantly higher in the female than in males. The findings are in agreement with the earlier reports (Omar *et al.*, 1983; Akintunde *et al.*, 1995), but contradictory to some of the results indicating thrombocytopenia. It was suggested that in evaluating results of hematological values in PTB, lymphopaenia rather than lymphocytosis, should be considered (Akintunde *et al.*, 1995).

The mean platelet count in normal Saudi adults (Al-Buhairan, 1998) was found to be higher ( $p < 0.05$ ) in females ( $283.0 \times 10^9/L$ ) as compared to normal males ( $256.0 \times 10^9/L$ ). A significant increase ( $p < 0.001$ ) in platelet count was observed in PTB patients as compared to the normal individuals. This finding showed thrombocytosis in PTB patients (Omar *et al.*, 1983) which was found relatively higher in female patients as compared to male PTB Saudi adults under current study. The cause for the observed thrombocytosis in PTB cases, might be attributed to an immune phenomenon due to production of platelets antibodies and to reactive myeloid hyperplasia (Omar *et al.*, 1983; Baynes *et al.*, 1987; Akintunde *et al.*, 1995). Earlier in several cases thrombocytopenia (platelets  $< 150 \times 10^9/L$ ) was reported in 24 out of 104 (23%) patients with tuberculosis (Maartens *et al.*, 1990). It was suggested, that thrombocytopenia might be due to the active tuberculosis and possible peripheral destruction of platelets by the bacterium (Chia and Machin, 1979; Al-Majed *et al.*, 1995) or hyperactive splenomegaly (Cassim *et al.*, 1993). The platelet count was also found

significantly higher ( $p < 0.001$ ) in Nigerian patients as compared to the control (Akintunde *et al.*, 1995; Awodu *et al.*, 2007).

Erythrocyte Sedimentation Rate (ESR), in untreated Saudi male and female PTB patients was found to be 70.13 and 77.5 mm h<sup>-1</sup>, respectively. These values are significantly higher than the standard normal values given (Hoffbrand and Pettit, 1993). The findings are fully supported by different reports specifying higher ESR values for PTB patients (Stenius-Aarniala and Tukiainen, 1979; Chia and Machin, 1979; Morris, 1989; Akintunde *et al.*, 1995; Olaniyi and Aken'Ova, 2003a, b; Awodu *et al.*, 2007).

In the present study, a significant reduction in anemia was observed after 6 weeks of treatment with antituberculosis drugs both in male and female PTB patients. The post-treatment hemoglobin levels were significantly higher ( $p < 0.001$ ) than the pre-treatment values in the patients. Similarly, the post-treatment hematocrit values were also found significantly ( $p < 0.001$ ) elevated as compared to the pre-treatment values of the PTB patients. The findings are in agreement with earlier reports where, anemia in PTB patients was found corrected by antituberculosis treatment (Morris *et al.*, 1989). Furthermore, the low grade anemia of chronic disorder was corrected without any need for iron or folic acid supplementation (Dosumu, 2001; Singh *et al.*, 2001; Qari, 2002; Das *et al.*, 2003; Singla *et al.*, 2003b; Awodu *et al.*, 2007; Bukhary and Alrajhi, 2007). However, in an earlier study the possibility of poor nutrition was suggested to be the cause of anemia (Bainton and Finch, 1964; Lombard and Masnvelt, 1993).

On the other side, leucocytosis observed initially in PTB patients included in the present study, became normal both in male and female patients after treatment with anti-tuberculosis drugs. The drop in total leucocyte count in both groups was associated with the sharp reduction in the neutrophil count after treatment. After 6 weeks of treatment hematological values also showed a significant increase in serum iron, total iron bonding capacity, transferring saturation values and improvement in other iron parameters in PTB patients as discussed in the earlier communication (Al-Omar and Oluboyede, 2002). During current study, there were no significant changes in both the pre-treatment and post-treatment serum and RBC folate levels.

## CONCLUSION

Based on the results of the present study, it was concluded that all such changes were associated to metabolic disorder accompanying chronic infections in

PTB patients. The varied hematological abnormalities observed in PTB patients suggested that the differential diagnosis of tuberculosis should be entertained in patients with varied hematological disorders and follow up protocol during treatment is to be observed.

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