The Prevalence of Absolute and Functional Iron Deficiency Anemia in New Cases of Smear-positive Pulmonary Tuberculosis and Their Sputum Conversion Rate at the End of Intensive Tuberculosis Treatment Phase

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Abstract: About one third of the population is infected with tuberculosis (TB). On the other hand, iron deficiency is the most common micronutrient deficiency in the world. A number of studies have documented anemia in patients with TB, however, this study aimed to assess the prevalence of iron deficiency anemia (IDA) in patients with acid-fast bacilli (AFB) sputum smear-positive, and sputum conversion in these two groups of patients with absolute and functional IDA at the end of the second month of anti-TB therapy in Zahedan, Iran. The results of this study revealed that 91 out of 198 (45.9%) sputum positive pulmonary TB patients were anemic, and among those 72 (79.1%) had iron deficiency anemia. The overall prevalence of IDA in this study was 36.3%. In 72 patients with IDA, 54 (75%) had functional while the

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remainder had absolute IDA 18 (25%). Twenty-one out of 72 (29.2%) of patients with IDA remained sputum positive and among 126 non IDA patients 47 (37.3%) had positive sputum smear at the end of intensive TB treatment phase (p=0.278). Approximately, less than half of patients with tuberculosis had anemia among them 79% had iron deficiency anemia. The frequency of functional IDA was three times more than absolute IDA. There was no statistically significant difference in sputum conversion between two groups of IDA and non-IDA patients after intensive phase of anti-TB therapy.

Introduction

Tuberculosis (TB) is still an important global health problem and kills about two million people annually. About a quarter of the world population is infected with TB (Moscow Declaration to End TB, 2017). Tuberculosis can present with a variety of hematological manifestations. A variety of factors have been suggested for TB-associated anemia, but the main causes attributed to it include suppression of erythropoiesis by inflammatory mediators, nutritional deficiency failure of iron utilization, and bone marrow suppression (Olaniyi and Aken'Ova, 2003; Lee et al., 2006; Zadeh et al., 2013).

Globally, iron deficiency is considered the most important contributor to the development of anemia, but other causes often coexist. Anemia has been reported in 16% to 94% of patients with pulmonary TB (Roberts et al., 1966; Cameron and Horne, 1971; Lee et al., 2006). In addition, it should be considered that iron deficiency has been associated with impaired immune function and reduced capacity to control infection (Dallman, 1987; Oppenheimer, 2001).

Functional iron deficiency is a state in which there is insufficient iron incorporation into erythroid precursors with adequate body iron stores which is detected by the presence of stainable iron in the bone marrow as well as a serum ferritin value within normal limits (Wish, 2006).

However, absolute iron deficiency anemia is characterized by low or absent bone marrow staining for iron and is distinguished from functional or relative iron deficiency, which is defined as a response to intravenous iron with an increase in hemoglobin (Hb) or a decrease in erythropoiesis-stimulating agent (ESA) requirement (Wish, 2006; Thomas et al., 2013).

If iron deficiency is an important factor related to TB-associated anemia, providing supplemental iron may be useful to increase blood hemoglobin concentrations and improve clinical outcomes in TB patients. Iron deficiency anemia was associated with a nearly 2-fold independent increase in the risk of death in a randomized clinical trial in patients with pulmonary TB in Tanzania, also showed that anemia at the initiation of tuberculosis therapy is responsible for delayed sputum conversion among pulmonary tuberculosis patients (Nagu et al., 2014).

Several studies have been conducted in this context to study the status of iron deficiency anemia in patients who had TB (Roberts et al., 1966; Cameron and

Horne, 1971; Oppenheimer, 2001). However, limited studies were carried out to demonstrate the type of IDA (functional and absolute) in TB patients and conversion rate after anti-TB treatment in these patients.

Therefore, this study aimed to investigate the prevalence of absolute and functional IDA in sputum smear-positive pulmonary TB patients and to demonstrate response to TB chemotherapy at the end of second month of treatment.

Material and Methods

This cross-sectional descriptive study was conducted between March 2016 and March 2017 in Zahedan, south-eastern Iran. After approving the project and getting approval from the Ethics Committee of Zahedan University of Medical Sciences, informed consent were obtained from all patients with the diagnosis of sputum smear-positive pulmonary tuberculosis and all of them were recruited into the study.

The inclusion criteria were as follow: smear-positive pulmonary tuberculosis patients over 14 years old with hemoglobin (Hb) less than 13 g/dl for male and less than 12 g/dl for female; and exclusion criteria were history of blood transfusion or blood donation in the last 3 months, history of recent iron supplementation, history of previous TB and anti-tuberculosis treatment, known chronic diseases such as hepatitis, AIDS, diabetes, cancer, or other inflammatory diseases, major and bilateral cavitary lesions in lungs, history of addiction, and Hb less than 9 g/dl. Functional iron deficiency anemia is defined as transferrin saturation (TSAT) less than 20% with ferritin levels above 40 micrograms per liter and absolute iron deficiency anemia is described as TSAT less than 20% with ferritin levels below 40 micrograms per liter (Hashemi et al., 2017).

For each patient, at the beginning of study and before standard anti-TB treatment (rifampin, pyrazinamide, isoniazid, and ethambutol), serum iron (SI), total iron binding capacity (TIBC), complete blood count (CBC), and ferritin, were requested. Patients who faced the criteria of IDA were divided into two groups of absolute or functional iron deficiency anemia according to Table 1. After two months of anti-TB treatment, three sputum smears were collected in three consecutive days, and the positive and negative cases were recorded using direct smear test and acid-fast staining. Finally, data obtained from the patients were analysed using descriptive statistics, chi-square and *t*-test in SPSS software (version 19, SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered significant.

Table 1 – Criteria for functional and absolute iron deficiency anemia

Parameters	Functional IDA	Absolute IDA
Hb	low	low
TSAT	low	low
Ferritin	normal-high	low

IDA – iron deficiency anemia; Hb – hemoglobin; TSAT – transferring saturation

Results

Overall, 217 patients were examined in this study amongst those 198 new smear-positive TB patients were enrolled according to inclusion and exclusion criteria. Ninety-one (45.9%) of the patients had anemia (hemoglobin below 13 g/dl in men and 12 g/dl in women). Based on IDA criteria and considering the transferrin saturation less than 20%, seventy-two out of 91 patients had iron deficiency anemia. Therefore, the overall prevalence of IDA was 36.3 percent.

The mean age of patients with IDA was 51.38 ± 14.88 years of whom 35 (48.6%) were male and 37 (51.4%) were female. The frequency of functional iron deficiency anemia was 54 (75%) and absolute IDA was reported 18 (25%). The comparison between functional and absolute IDA, based on gender, age and duration of TB symptoms before treatment were not significantly different in TB patients (p=0.341, p=0.887, p=0.750, respectively) (Table 2).

At the end of two-month anti-TB therapy, 68 patients remained smear positive (37.3% with IDA compared to 29.2% without IDA). The difference of sputum conversion in TB patients with and without IDA was not statistically significant (p=0.278) (Table 3).

Table 2 – Distribution of gender, mean age and duration of symptoms in sputum smear-positive tuberculosis patients with iron deficiency anemia

		Functional IDA	Absolute IDA	Total	P-value
Gender	male	28 (51.9%)	7 (38.9%)	35 (48.6%)	0.341
	female	26 (48.1%)	11 (61.1%)	37 (51.4%)	
	total	54 (100%)	18 (100%)	72 (100%)	
Age (year) ± SD		51.44 ± 13.99	51.94 ± 13.16	51.37 ± 14.88	0.877
Duration of symptoms (day) ± SD		24.70 ± 8.07	24.00 ± 8.06	24.38 ± 7.66	0.750

IDA – iron deficiency anemia; SD – standard deviation

Table 3 – Sputum conversion rate at the end of the second month in TB patients with and without iron deficiency anemia

Smear results	IDA	Non-IDA	Total	P-value
+	21 (29.2%)	47 (37.3%)	68 (34.3%)	0.278
–	51 (70.8%)	79 (62.7%)	130 (65.7%)	
total	72 (100%)	126 (100%)	198 (100%)	

TB – tuberculosis; IDA – iron deficiency anemia

Table 4 – Sputum conversion rate of positive smear at the end of the second month in TB patients with functional and absolute IDA

Smear results	Functional IDA	Absolute IDA	Total	P-value
+	15 (27.8%)	6 (33.3%)	21 (29.2%)	
–	39 (72.2%)	12 (66.7%)	51 (70.8%)	0.766
total	54 (100%)	18 (100%)	72 (100%)	

TB – tuberculosis; IDA – iron deficiency anemia

The frequency of positive sputum smear after 2 months of treatment with anti-TB in patients with functional and absolute IDA was 15 (27.8%) and 6 (33.3%), respectively with no significant difference (p=0.766) (Table 4).

Discussion

Tuberculosis remains a public health threat, especially in developing countries and is still a major cause of death and suffering worldwide. This devastating disease is much higher among people infected with HIV, and also higher among people affected by risk factors such as under-nutrition, diabetes and smoking (Antonucci et al., 1995; Espinal et al., 2000; Ferrara et al., 2012). On the other hand, anemia is also a major public health problem in many parts of the world. According to a study done by World Health Organization (WHO) on anemia, worldwide prevalence of anemia was 25% from 1993 to 2005 (World Health Organization, 2008). Nutritional anemia is a serious health problem globally which is primarily due to iron deficiency. The prevalence of anemia in all patients with TB was reported between 30–94% in several studies (Cameron and Horne, 1971; Oppenheimer, 2001; Lee et al., 2006). Iron deficiency may also contribute to the development of TB disease because iron deficiency compromises the immune function and reduced body capacity against infection control.

In our study we evaluated TB patients who had IDA in Zahedan, a big city situated in Sistan and Baluchestan, south-eastern Iran with the highest prevalence of TB in Iran. The incidence of all form of TB and sputum smear positive pulmonary TB was estimated 30.21 and, 19.03 per 100,000 populations, respectively in the year 2017 in Zahedan (Center for Disease Control and Prevention, 2019).

Based on the results of this study it was found that nearly half of our patients were anemic and most of them (79.1%) had IDA. The overall prevalence of iron deficiency anemia in this study was 36.3%.

According to the study done by Isanaka et al. (2012), the overall prevalence of anemia in TB patients was 64% that more than one-half of them were related to IDA. The results of this study showed no association between overall anemia or iron deficiency anemia at baseline and the risk of treatment failure at 1 month after initiation. The prevalence of anemia in our study was less than the mentioned study,

but similar to our study, the majority of the patients had IDA and we did not found any association between two groups of IDA and non-IDA for sputum conversion.

In a study conducted by Lee et al. (2006), anemia was mostly associated with the female and older age and during or after anti-TB treatment, anemia was resolved in 64.6% of patients without iron intake. On the contrary, we did not find any significant relationship based on gender in the two groups of IDA and non-IDA patients and the mean ages of our patients were similar.

In another study, in female with pulmonary tuberculosis in their reproductive age, 67.5% had IDA and using tardiferon helped in enhancing the efficiency of treatment for tuberculosis in the presence of IDA (Mukhtarov and Sultanova, 2009).

It seems that geographical areas and nutritional base of the patients play important roles to determine the prevalence of IDA in TB patients and subsequently, predict their response to tuberculosis treatment (Cegielski and McMurray, 2004; Mulenga et al., 2017). Approximately, more than one-third of our TB patients had IDA and it seems reasonable that most of them owned the criteria for functional IDA which is more prevalent than absolute IDA. Expectedly, functional iron deficiency is much more prevalent than absolute iron deficiency. Based on epidemiological studies on iron deficiency showed prevalence rates varying between 29–46% for functional iron deficiency and for iron deficiency-associated anemia prevalence rates between 7–42% (Kuvibidila et al., 2004; Ludwig et al., 2013).

Being underweight has been associated with a higher risk of tuberculosis in developing countries. The fact that undernourishment can also influence iron metabolism, it would have been better to calculate BMI (body mass index) which is one of the limitations of this study.

Although the results of our study did not show any association between sputum conversion and treatment response in IDA and non-IDA patients, further research with larger sample size in different geographical regions is required to increase reliability of the studies.

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References

Antonucci, G., Girardi, E., Raviglione, M. C., Ippolito, G. (1995) Risk factors for tuberculosis in HIV-infected persons: a prospective cohort study. *J. Am. Med. Assoc.* **274(2)**, 143–148.

Cameron, S. J., Horne, N. W. (1971) The effect of tuberculosis and its treatment on erythropoiesis and folate activity. *Tubercle* **52**, 37–48.

Cegielski, J. P., McMurray, D. N. (2004) The relationship between malnutrition and tuberculosis evidence from studies in humans and experimental animals. *Int. J. Tuberc. Lung Dis.* **8**, 286–298.

Center for Disease Control and Prevention (2019) *Tuberculosis Status*. Center for Disease Control and Prevention (Division of TB and Leprosy Elimination), Ministry of Health and Medical Education, Iran. Available at: http://tb-lep.behdasht.gov.ir/TB_Situation_in_Iran.aspx (in Persian)

Dallman, P. R. (1987) Iron deficiency and the immune response. *Am. J. Clin. Nutr.* **46**, 329–334.

Espinal, M. A., Peréz, E. N., Baéz, J., Hénriquez, L., Fernández, K., Lopez, M., Olivo, P., Reingold, A. L. (2000) Infectiousness of Mycobacterium tuberculosis in HIV-1-infected patients with tuberculosis: a prospective study. *Lancet* **355(9200)**, 275–280.

Ferrara, G., Murray, M., Winthrop, K., Centis, R., Sotgiu, G., Migliori, G. B., Maeurer, M., Zumla, A. (2012) May risk factors associated with pulmonary tuberculosis: smoking, diabetes and anti-TNFα drugs. *Curr. Opin. Pulm. Med*. **18(3)**, 233–240.

Hashemi, S. M., Mashhadi, M. A., Mohammadi, M., Ebrahimi, M., Allahyari, A. (2017) Absolute and functional iron deficiency anemia among different tumors in cancer patients in south part of Iran. *Int. J. Hematol. Oncol. Stem Cell Res*. **11(3)**, 192–198.

Isanaka, S., Mugusi, F., Urassa, W., Willett, W. C., Bosch, R. J., Villamor, E., Spiegelman, D., Duggan, C., Fawzi, W. W. (2012) Iron deficiency and anemia predict mortality in patients with tuberculosis. *J. Nutr*. **142(2)**, 350–357.

Kuvibidila, S. R., Gauthier, T., Rayford, W. (2004) Serum ferritin levels and transferrin saturation in men with prostate cancer. *J. Natl. Med. Assoc*. **96**, 641–649.

Lee, S. W., Kang, Y. A., Yoon, Y. S., Um, S. W., Lee, S. M., Yoo, C. G., Kim, Y. W., Han, S. K., Shim, Y. S., Yim, J. J. (2006) The prevalence and evolution of anemia associated with tuberculosis. *J. Korean Med. Sci*. **21(6)**, 1028–1032.

Ludwig, H., Müldür, E., Endler, G., Hübl, W. (2013) Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. *Ann. Oncol*. **24(7)**, 1886–1892.

Moscow Declaration to End TB (2017) *First WHO Global Ministerial Conference on Ending TB in the Sustainable Development Era: A Multisectoral Response*. Geneva, World Health Organization and the Ministry of Health of the Russian Federation. Available at: https://www.who.int/tb/features_archive/Moscow_Declaration_to_End_TB_final_ENGLISH.pdf?ua=1

Mukhtarov, D. Z., Sultanova, R. A. (2009) The specific features of the clinical course of tuberculosis and enhancement of its treatment efficiency in fertile-age women with iron-deficiency anemia. *Tuberk. Biolezni Legkih* **2009(12)**, 45–50. (in Russian)

Mulenga, C. M., Kayembe, J. M. N., Kabengele, B. O., Bakebe, A. (2017) Anemia and hematologic characteristics in newly diagnosed pulmonary tuberculosis patients at diagnosis in Kinshasa. *J. Tuberc. Res*. **5**, 243–257.

Nagu, T. J., Spiegelman, D., Hertzmark, E., Aboud, S., Makani, J., Matee, M. I., Fawzi, W., Mugusi, F. (2014) Anemia at the initiation of tuberculosis therapy is associated with delayed sputum conversion among pulmonary tuberculosis patients in Dar-Es-Salaam, Tanzania. *PLoS One* **9**, e91229.

Olaniyi, J. A., Aken'Ova, Y. A. (2003) Haematological profile of patients with pulmonary tuberculosis in Ibadan, Nigeria. *Afr. J. Med. Sci*. **32(3)**, 239–242.

Oppenheimer, S. J. (2001) Iron and its relation to immunity and infectious disease. *J. Nutr*. **131**, 616S–636S.

Roberts, P. D., Hoffbrand, A. V., Mollin, D. L. (1966) Iron and folate metabolism in tuberculosis. *Br. Med. J*. **5507**, 198–202.

Thomas, D. W., Hinchliffe, R. F., Briggs, C., Macdougall, I. C., Littlewood, T., Cavill, I.; British Committee for Standards in Haematology (2013) Guideline for the laboratory diagnosis of functional iron deficiency. *Br. J. Haematol*. **161(5)**, 639–648.

Wish, J. B. (2006) Assessing iron status: Beyond serum ferritin and transferrin saturation. *Clin. J. Am. Soc. Nephrol*. **1**, S4–S8 (Suppl. 1).

World Health Organization (2008) *Worldwide Prevalence of Anaemia 1993–2005. WHO Global Database on Anaemia*. Available at: http://www.who.int/iris/handle/10665/43894

Zadeh, J. H., Nasehi, M., Rezaianzadeh, A., Tabatabaee, H., Rajaeifard, A., Ghaderi, E. (2013) Pattern of reported tuberculosis cases in Iran 2009–2010. *Iran. J. Public Health* **42(1)**, 72–78.