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(RESEARCH ARTICLE)

Nutritional background of low-income pulmonary tuberculosis patients on anti-tuberculosis therapy at Infectious Disease Hospital, Calabar, Nigeria: A case-control study

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Abstract

Background: Poverty and malnutrition are associated with the risk of developing tuberculosis (TB). Nutritional reintegration with anti-TB therapy may improve treatment success rate.

Aim: To investigate the nutritional status of low-income pulmonary TB patients in relation to the different anti-TB treatment phases.

Methods: Forty five pulmonary TB patients and 40 controls aged 19-54 years, receiving treatment at Infectious Disease Hospital, Calabar, Nigeria, between September 2018 and July 2019 were studied. Serum total protein, albumin, iron and vitamin A were determined by colorimetric and HPLC methods respectively. Height and weight were measured and BMI computed, and data analysed using Student's t-test, ANOVA, and Pearson's correlation at $P<0.05$.

Results: Among TB patients, 66.7%, 35.5%, and 22.22% were albumin, iron, and vitamin A deficient respectively. Total protein and globulins levels were higher while BMI, albumin, iron, and vitamin A were lower in the TB patients compared to the control ($P=0.001$). Albumin and iron levels of TB patients on continuation phase of anti-TB treatment (CPAT) were higher than those of TB-HIV coinfection on the same phase of treatment, TB patients on intensive phase of anti-TB treatment (IPAT) and controls ($p<0.05$). Comparing TB patients on CPAT and IPAT, also CPAT-HIV and IPAT-HIV patients, BMI and biochemical indices studied were not significantly different ($P>0.05$) respectively. Albumin and iron were significantly lower in CPAT-HIV compared with CPAT patients. Albumin correlated positively and significantly with iron ($r=0.405$, $p=0.006$) in TB patients.

Conclusion: Tuberculosis is associated with decreased BMI, albumin, iron and vitamin A, and higher total protein, and globulin, suggesting that malnutrition may be associated with TB risk, poor treatment compliance and outcomes.

Keywords: Pulmonary tuberculosis; Malnutrition; Low income; Anti-TB therapy

1. Introduction

Tuberculosis (TB) and malnutrition are public health concern of people living in developing countries. The association of poverty with both under-nutrition and TB due to food insecurity, lack of access to basic health services, and poor living conditions which fuels TB transmission has long been described [1]. Besides playing a significant role in the

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general well-being, adequate nutrition is essential to healing from infections like mycobacterium tuberculosis. The poverty traumatized group unbecomingly suffer from high rates of under-nutrition, which impact both on the risk for development of TB disease and unfavourably affect outcomes of TB treatment. Most of the infections with mycobacterium tuberculosis (TB) occur without the associated symptoms, known as latent tuberculosis [2]. Approximately only 10 percent of individuals infected with TB progress to active TB disease during their lifetime; the remainder of persons infected successfully contain the infection [3, 4]. Globally, an estimated 10 million people developed active TB disease in 2019, with 1.4 million TB deaths [5].

Mycobacterium tuberculosis has evolved numerous tactics to escape host immune defence and anti-TB treatment attack via becoming inactive (latent state within the human host) and to reactivate later in life. The association between TB and malnutrition is bi-directional, TB leads the patient to malnutrition, and malnutrition intensifies the risk of developing active TB by 6-10 fold. Undernutrition weakens the human immune system and this can result in latent TB developing into active infection [6]. On the other hand, TB worsens undernutrition by increasing metabolic demand and decreasing appetite [7]. Improving the nutrition of an individual significantly reduces tuberculosis risk. Thus, malnutrition is an important modifiable risk factor for the prevention of development of tuberculosis (TB). Patients with tuberculosis experience loss of appetite, nutrient malabsorption, micronutrient malabsorption, and altered metabolism resulting in wasting. Underweight is a malnutrition stage in which the body mass index (BMI) of adult scores less than 18.5 kg/m^2 cuts-points [6]. Underweight results from an imbalance between the supply of food and the body's demand for the nutrients. The treatment outcomes of TB patients can be enhanced by monitoring their nutritional status. Malnutrition is a state of sustenance typified by the deficiency, excess, or imbalance in the energy and/or nutritional intake of a person. On the African continent, 29 - 61% of TB patients are malnourished [8, 9].

Micronutrients such as iron, vitamin A are central to the biology of mycobacterium tuberculosis. Iron is a vital nutrient for bacterial growth, replication, metabolism and virulence [10]. The human host stores iron bound to various proteins such as hemoglobin, haptoglobin, transferrin, ferritin, and lactoferrin. Also at biological pH iron has a low solubility. This limits the accessibility of free iron for pathogenic bacteria by a process called nutritional immunity [11-15]. Iron seizure is a key element of the mammalian innate immune system, and humans have dedicated proteins that scavenge extracellular iron to prevent its uptake by pathogens [16]. While bacteria have developed complex pathways to steal iron from host proteins, in order to circumvent this, humans have evolved proteins to neutralize bacterial iron-scavenging pathways staging a struggle for iron between the human host and bacteria. Studies on iron and TB have defined host iron levels and predisposition to TB; presenting enhanced multiplication of the pathogen and disease development following administration of iron that overrides the response of the mammalian host to limit iron during an infection [17]. Another factor that enhances the spread of TB is deficiency in nutrients, such as vitamin A (retinol), especially widespread in high TB endemic regions [18].

Low serum levels of retinol, the circulating form of vitamin A, have been reported to correlate with a 10-fold increased risk and susceptibility to TB [19]. Also, the bioactive form of vitamin A, all-trans retinoic acid, induces antimicrobial activity in M. tuberculosis-infected macrophages [20].

Tuberculosis is common in developing countries where a good number of the population may also be malnourished. Whether existing nutritional status is a determinant of treatment outcomes among the TB patients in a resource-limited setting is not fully clear. The nutritional component of anti-TB treatment is often neglected, and this may pose a risk to TB recurrence and poor treatment outcomes. Studies on nutritional status of TB patients are common, however, studies assessing nutritional status of TB patients on various treatment phases are scarce. Also, evaluation of the nutritional status of TB patients on various anti-TB treatment phases and TB-HIV coinfection may identify those at risk of treatment failure. In the current study, we assessed the levels of iron, total protein, albumin, globulins and Vitamin A in patients with pulmonary tuberculosis in relation to the different anti-TB treatment phases.

2. Material and methods

2.1. Ethical consideration

This study was carried out in accordance with the ethical principles for Medical Research involving human subjects as outlined in the Helsinki Declaration in 1975 and subsequent revisions. The study protocol was approved by the Health Research Ethics Committee, Ministry of Health, Cross River State, with protocol assigned number, REC. NO. (RP/REC/2015/266). A written informed consent was obtained from all individual study participant, after explaining the purpose of the study. The confidentiality of the information was preserved at all steps. The rights to withdraw from participation in the study at any point in time were respected.

2.2. Study design

This case-control study was conducted in Calabar Metropolis, among pulmonary tuberculosis patients admitted into Infectious Diseases Hospital, Calabar, Cross River State, and Southern Nigeria. The TB patients were categorized further based on the phase of anti-TB treatment and HIV co-infection into those on initiation (intensive) phase, continuation phase, initiation phase co-infected with HIV and continuation phase co-infected with HIV.

2.3. Study setting

All pulmonary TB patients in the ages between 19 to 54 years, who were receiving the directly observed therapy short course strategy (DOTS) in the Infectious Diseases Hospital, Calabar, between September 2018 and July 2019 were recruited into the study. The population consists of TB patients in Calabar Metropolis, comprising of residents of Calabar South and Calabar Municipal Local Government areas, South-South, Nigeria.

2.4. Participants and inclusion criteria

The study participants included pulmonary TB patients living in Calabar Metropolis and non-TB controls who were living in the same geographic area. Patients with confirmed cases of pulmonary TB admitted into the Infectious Disease Hospital, who were receiving the directly observed therapy short course strategy (DOTS) and with monthly income below =N=23,000 (<US$46) were considered living below the poverty line and who gave written informed consent were recruited into the study. Patients with monthly income above =N=23,000 were excluded from the study. Patients not willing to participate in the study and TB patients unable to communicate properly were excluded. Patients with extra-pulmonary disease, multidrug-resistant tuberculosis, were excluded from the study.

2.5. Data collection

After overnight fasting, a standard venepuncture method was used to obtain 5 mL of blood from all the participants. The blood was dispensed into plain containers, and allowed to clot and then centrifuged at 3 000 rpm for 5 minutes at room temperature. The sera were separated immediately into aliquots using sterile Pasteur pipettes and stored at −20 °C in the laboratory of the health facility until analysis. Patients' information on general health, history of past diseases and addictions were collected by a face-to-face patient interview using a structured questionnaire. The information collected from the patients included socio-demographic characteristics (such as age, gender, marital status, education, monthly income, habits such as smoking, consumption of alcohol) and bio-clinical information such as disease duration, treatment phase and BMI. A medical weighing scale was used to measure the weight of each participant to the nearest 0.1 kg. Height was measured using a measuring tape on a vertical rod to the nearest 0.1 cm. Body mass index was computed as the ratio of weight (kg) to height (m^2). Body mass index less than 18.5kg/m^2 was considered underweight. Normal weight was a BMI of 18.50-24.99 kg/m2, the overweight had a BMI of 25.00-29.99 kg/m2, and the obese had a BMI ≥30.00 kg/m2 [21]

2.6. Data sources/Laboratory measurement

2.6.1. Serum vitamin A concentration was estimated by HPLC-UV method.

In this method, retinol is separated from other substances which absorb radiant energy at equal or similar wavelengths to retinol. Retinol is then detected using spectrophotometric techniques. For the determination of retinol, an internal standard and the precipitation reagent are added. During the precipitation step, high molecular substances are removed. After centrifugation the supernatant is injected into the HPLC system. The isocratic separation via HPLC at 30° C uses a "reversed phase" column. The chromatograms are recorded by a UV detector at 325 nm. The quantification is performed with the delivered plasma calibrator, the concentration is calculated by the internal standard method via integration of the peak heights resp. peak areas [22].

$$Conc.sample = \frac{peak\ area\ patient\ sample * conc.calibrator * F}{peak\ area\ calibrator}$$

$$F = \frac{Peak\ area\ internal\ Standard\ of\ the\ calibrator}{Peak\ area\ analyte\ of\ the\ calibrator}$$

2.6.2. Estimation of total protein by biurets colorimetric method

The biuret method is based on the reaction of protein with copper ions to form a coloured complex whose absorption in the presence of excess copper, is proportional to the amount of protein present. The absorbance of specimen and standard are measured against reagent blank at 546 nm [23].

$$Tot.Prot.Concentration\ in\ sample\ = \frac{Absorbance\ of\ sample\ x\ Standard\ concentration\ of\ protein}{Absorbance\ of\ protein\ standard}$$

2.6.3. Estimation of albumin by modified Bromocresol green colorimetric method

Albumin concentration was determined by modified Bromocresol green colorimetric method. Measurement of albumin is based on its binding to the indicator dye bromocresol green (BCG) at pH 4.1 to form a blue-green colored complex. The intensity of the blue-green color is directly proportional to the concentration of albumin in the sample. The absorbance of specimen (A specimen) and standard (A standard) are measured against reagent blank at 578nm [24].

$$Albumin\ concentration\ (g/dL)\ = \frac{Absorbance\ of\ specimen\ x\ concentration\ of\ standard}{Absorbance\ of\ standard}$$

Globulin concentration was computed by subtracting albumin concentration from total protein concentration.

2.6.4. Serum iron concentration was determined by colorimetric method.

Serum sample added to a reagent containing ferric iron (Fe^{3+}) in acetate buffer at pH 4.5 causes Fe^{3+} to be released from transferrin because of the low pH which then forms a coloured complex which is measures spectrophotometrically using a reagent black at 500nm [25]

$$Total\ iron\ = \frac{A^2\ test\ -\ A1\ test\ \times\ conc.of\ standard}{A2\ standard\ -\ A^1\ standard}$$

A^1 = absorbance of the tubes before addition of iron color reagent, A^2= absorbance of the tubes after addition of iron color reagent.

2.7. Study size

Sample size was determined according to the method of Sullivan [26], using the formula $\frac{(Z_\alpha+Z_\beta)^2.\bar{p}(1-\bar{p})}{(p0-p1)2}$. The power of 0.84 was calculated at beta error 80%. The sample size of 53 patients was arrived at. However, due to some patients not being able to fulfill all the criteria for inclusion during the period of this study, 45 patients were selected for the study. A total of 85 participants, comprising of 45 pulmonary TB patients and 40 non- TB controls were selected for the study.

2.8. Statistical analyses

Results were presented as mean ± standard deviation. Data were analyzed using the statistical package for social sciences (SPSS version 23.0, IBM, USA). One way analysis of variance (ANOVA) was used to test the variations within and among group means and Fisher's least significant difference (LSD) post-hoc test was used for the comparison of multiple group means. Pearson's correlation was used to determine the associations between variables.The significance level of the tests was set at α=0.05.

3. Results

3.1. Participants

A total of 53 pulmonary TB participants were eligible but because of non-compliance 45 patients and 40 controls were recruited for this study.

3.2. Descriptive data

The profile of TB patients is as shown in table 1, in this study 35.56% of the TB infected study participants were females while 64.44% were males. Twenty six of the TB infected participants (57.78%) were HIV negative while nineteen of the TB infected participants (42.22%) were co-infected with HIV and were of younger average age. Thirty (66.7%), Sixteen (35.5%), and ten (22.22%) of the patients were albumin, iron, and vitamin A deficient respectively. Vitamin A deficiency is defined as vitamin A levels less than 32.5mcg/dL in adults. Iron and albumin deficiencies are defined as less than 60mcg/dl and 3.4g/dl respectively.

3.3. Main results

The comparison of Age, BMI, serum iron, vitamin A, total protein, albumin and globulins in the different phases of anti-TB treatment with or without HIV coinfection and controls were shown in table 2. Age, BMI, albumin, total proteins, globulins, iron and vitamin A concentrations varied significantly (P<0.05) among TB patients on intensive phase of anti-TB treatment without HIV coinfection (IPAT), TB-HIV co-infected patients on intensive phase of anti-TB treatment, TB patients on continuation phase of anti-TB treatment (CPAT) without HIV coinfection, TB-HIV co-infected patients on continuation phase of anti-TB treatment and the controls. A correlation between albumin and iron is depicted in figure 1. Albumin and iron correlated positively (r=0.405, p=0.006) in TB patients. A correlation between vitamin A and iron in TB patients is shown in figure 2. Vitamin A and iron correlated negatively (r= -0.040, *P* =0.040). A Correlation between Age and iron in TB patients is shown in figure 3. Age correlated positively with iron (r = 0.303, P=0.043).

Table 1 Profile of TB patients studied

	Population profile		**Frequency**	**Percentage**
1	Sex	Males	29	64.44
		Females	16	35.56
2	Age	<25	13	28.88
		>25	32	71.12
3	HIV status	Negative(mean age=36.38)	26	57.78
		Positive(mean age=27.95)	19	42.22
4	Occupation	Farmers	20	44.45
		others	25	55.55
5	Iron status	Deficient <60mcg/dl	16	35.50
		Normal(60-170)mcg/dL	29	64.50
6	Albumin status	Deficient <3.4g/dl	30	66.70
		Normal (3.4-5.4)g/dL	15	33.30
7	Vitamin A status	Deficient <33mcg/dl	10	22.22
		Normal (33-60)mcg/dl	35	77.78

Table 2 Age, BMI, serum iron, vitamin A, total protein, albumin and globulins in the different phases of anti-TB treatment with or without HIV co-infection and controls

Parameters	**TB patient on IPAT without HIV coinfection (n=7)**	**TB-HIV co-infected patients on IPAT (n=6)**	**TB patients on CPAT without HIV coinfection (n=19)**	**TB-HIV co-infected patients on CPAT (n=13)**	**None-TB Controls (40)**	**F-ratio**	**P-value**
Age(years)	42.57±10.09e	26.00±2.37	34.11±12.12	28.85±7.30	31.45±7.49	3.994	0.005*
BMI(kg/m^2)	15.59±1.15bd	14.63±0.63	15.87±1.14	15.85±1.33	22.16±2.78	50.365	<0.001*
Total protein (ug/dl)	9.50±0.51d	9.00±0.47	9.46±0.93	9.23±0.68	7.71±0.98	18.464	<0.001*
Albumin(g/dl)	3.33±0.33	2.90±0.49	3.35±0.24acd	2.85±0.43	4.09±0.16	71.369	<0.001*
Globulin(g/dl)	6.17±0.53	6.03±0.54	6.12±0.94d	6.38±0.56	3.60±0.97	47.760	<0.001*
Iron (ug/dl)	75.06±16.33	44.13±23.00	82.94±16.36acd	46.99±18.23	137.87±42.26	29.623	<0.001*
Vitamin A (ug/dl)	39.47±3.94	39.90±5.92	37.04±5.93d	40.81±5.65	69.38±5.34	165.278	<0.001*

Result presented as mean ± SD, * significant at $P<0.05$, a=significant difference between TB patients on CPAT without HIV coinfection and TB-HIV co-infected patients on CPAT, b= significant difference between TB patients on CPAT, IPAT both without HIV co-infection and controls, c= significant difference between TB patients on CPAT without HIV coinfection and TB-HIV coinfection on IPAT, d= significant difference between TB patients on CPAT without HIV coinfection, TB-HIV patients on CPAT, TB patients on IPAT without HIV coinfection, TB-HIV coinfection on IPAT and controls, e= significant difference between TB patients on CPAT without HIV coinfection, TB-HIV coinfection on CPAT, TB-HIV coinfection on IPAT and TB patients on IPAT without HIV coinfection, TB=tuberculosis, HIV= human immunodeficiency virus, BMI=body mass index, CPAT=continuation phase of anti-TB treatment, IPAT=intensive phase of anti-TB treatment.

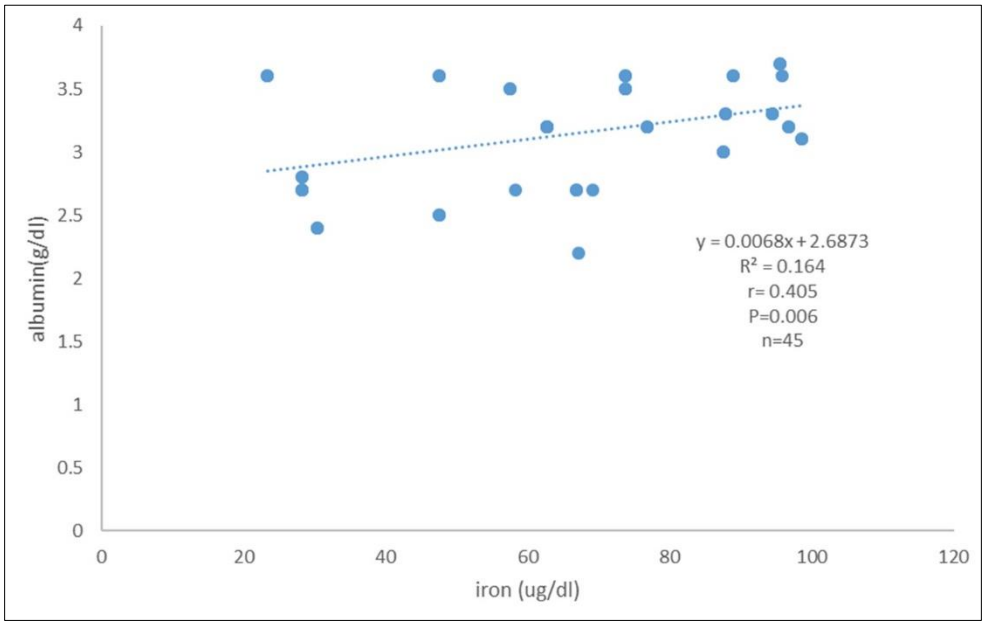

Figure 1 Correlation between albumin and iron in TB patients

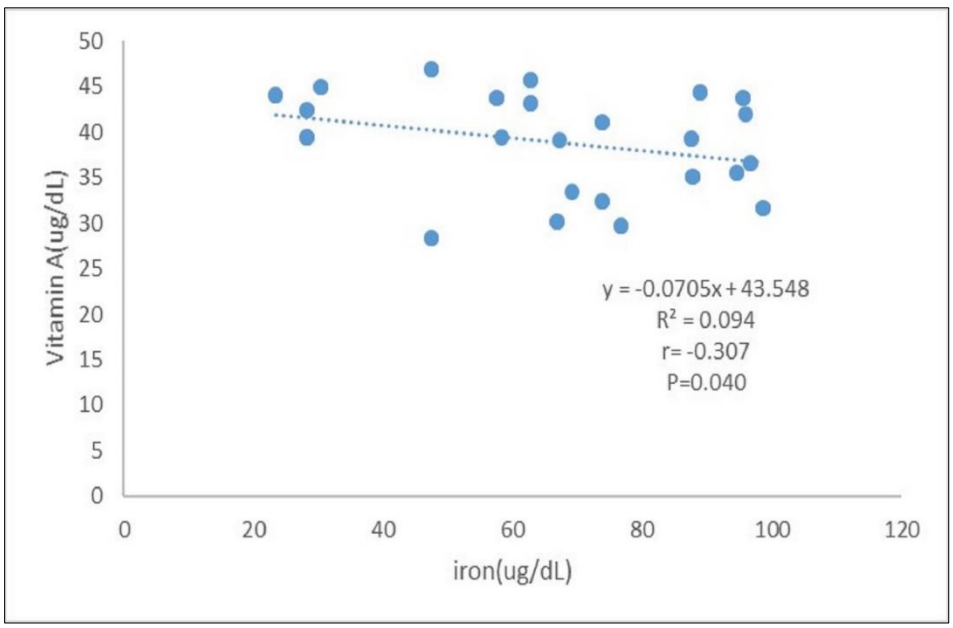

Figure 2 Correlation between vitamin A and iron in TB patients

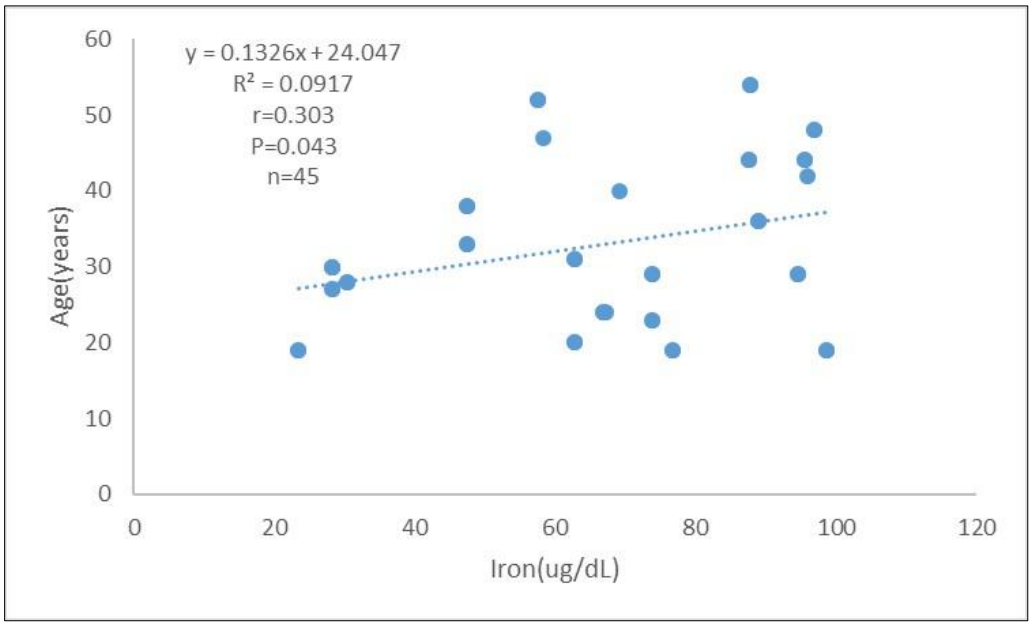

Figure 3 Correlation between Age and iron in TB patients

4. Discussion

This study examined the levels of serum iron, vitamin A, total protein, albumin and globulins in patients with pulmonary tuberculosis. The significantly higher body mass index in non-TB control compared to the patients with pulmonary TB may be as a result of wasting associated with TB infection. Infection with mycobacterium tuberculosis causes weight loss via wasting and macro/micro-nutrient deficiency, as a result of loss of appetite and malabsorption. This observation is in line with that of Magassouba, *et al.*, [27], who reported that most patients with active TB experience weight loss caused by numerous factors, including decreased dietary intake due to loss of appetite, nausea, and abdominal pain. The bidirectional relationship between undernutrition and TB leads to a high prevalence of undernutrition among people with TB, as well as an increased incidence of TB reactivation among the undernourished persons with latent infection. Reactivation of latent TB among the malnourished may pose a challenge to TB eradication, which underscores the impact of poverty on policy implementation. The higher BMI in TB patients in the continuation phase of anti-TB treatment compared to those in intensive phase of anti-TB treatment may suggest nutritional improvement following anti-TB chemotherapeutic suppression of the pathogen.

The lower concentration of albumin in the TB patients compared to the controls may indicate the underlying malnutrition in these patients. Also albumin is a negative acute phase reactant protein, with decreasing levels seen in these patient due to the associated inflammation in this condition. In the TB patients, those co-infected with HIV had lower albumin level compared to the TB patients not infected with HIV, suggesting further perturbation in albumin level in the TB-HIV co-infected group related to malnutrition and a higher degree of inflammation. This finding is similar to that of Alvarez-Uria *et al.,* [28], who observed that hypoalbuminemia is associated with an increased risk of mortality in patients with tuberculosis and that serum albumin can be a useful low-cost diagnostic marker for tuberculosis in HIV infected patients qualified for treatment. The higher globulin level in the TB patients may be as a result of increase production of immunoglobulins due to the infection.

The lower level of iron in the TB patients compared to the control may suggest micronutrient deficiencies associated with TB infection as well as malnutrition related deficiency in iron binding proteins. Also, the mammalian host ability to withheld iron availability to the pathogen to limit their virulence may contribute to lower iron in the TB patients. This observation is similar to that of Cobelens & Kerkhoff [29], in their report that anemia is an early marker of TB pathology which develops in the months that precedes clinical TB disease. Mycobacterium tuberculosis patients in the continuation phase of anti-TB treatment had higher iron compared to those on intensive phase of treatment, indicating gradual improvement in micronutrients following anti-TB chemotherapy pathogen suppression. The cause of iron deficiency in TB patients may be multifaceted and management of iron deficiency may be difficult if the fundamental cause is not ruled out. Anaemia in these patients may be due to inflammation (anaemia of inflammation (AI), nutritional anaemia or a combination of both, the most common cause in these patients being iron deficiency. Other micronutrients contributing to the formation of normal levels haemoglobin include copper, zinc, magnesium, cobalt, molybdenum,

vitamins, especially folic acid and vitamin B12; and amino acids. Therefore, nutritional anemia may only be overcome if the respective deficiencies in these nutrients are precisely determined and corrected as well. This finding is in accordance to that by Minchella *et al*., [30], who reported that TB disease likely drives the development of anemia, instead of the other way around, since anemia generally resolves following TB therapy. The further decrease in iron level in the HIV-associated tuberculosis patients compared to the TB only infected patients may suggest extensive malnutrition in this group of patients together with a heightened demand for iron by the two pathogens and the additional iron withholding by the host joined with associated inflammations in these infections. This observation is in line with that of Armitage and Drakesmith [31], who reported that anemia of inflammation (AI) is frequently observed during chronic inflammatory and infectious conditions, including mycobacterium tuberculosis (tb) infection. Absolute iron deficiency anaemia in these patients may be due to a direct consequence of poverty, malnutrition, and decreased appetite. The significant positive correlation between iron and albumin TB patients suggest that both albumin and iron are good markers of nutritional landscape and indicators of disease severity in these patients. Nutritional improvement in these patients following anti-TB treatment bacterial suppression, may be associated with concurrent rise in these cursors, hence, may be useful in monitoring and predicting outcomes in these patients. The significant positive correlation between iron and age may suggest higher iron levels in the older cohort of TB in this study, due to a higher prevalence of TB-HIV coinfection which places a higher demand on iron in this younger group compared to the older group with few cases of TB-HIV coinfections in this study. The significant negative correlation between iron and vitamin A may suggest that vitamin A is stored in muscles and the older patients with lower muscle mass invariably have higher iron stores in these patients.

The lower level of vitamin A in TB patients compared to the control may suggest micronutrient deficiency in these patients due to malnutrition. Micronutrient deficiency is both a risk for reactivation of latent TB infection and development of complications, including treatment failures, recurrence and death due to infection.

Limitation of the study

The study is limited by its sample size, as some patients did not fulfill the criteria for inclusion during the period of the study. Also, access to patients' information before they commenced anti-TB treatment was limited and this hindered availability of baseline data on the nutritional status of these patients prior to initiation of treatment.

5. Conclusion

The findings of increased globulin, decreased albumin, BMI, vitamin A and iron in tuberculosis may be related to the severity of the disease and may hinder treatment compliance and outcomes. Nutritional status improves with TB treatment while malnutrition worsens in TB patients with HIV-coinfection. Poverty affect nutritional status of individuals, hence, the administration of the anti-TB drugs concurrently with stringent nutritional intervention may improve treatment success rate.

Compliance with ethical standards

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Authors' contributions

E.R.E., A.C.N and E.P.U conceptualized the study, designed the study, collected and analysed data, interpreted data, prepared and the reviewed manuscript for the final submission and conducted the research. U.A.F, PAA and E.P.U Contributed to collecting the data, conducted the costing analysis, editing manuscript for the final submission. E.R.E., PAA and U.A.F. provided technical input, revised and validated the manuscript for the final submission. E.R.E. supervised the study by providing leadership and oversight as the project leader. All the authors have read and agreed to the final manuscript.

Disclosure of conflict of interest

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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