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Original article

Micronutrient levels of tuberculosis patients during the intensive phase, a prospective cohort study

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SUMMARY

Introduction: The objectives of this study were to estimate the micronutrient deficiency levels of tuberculosis patients at the start and end of the intensive phase, and to identify the predictors of micronutrient deficiencies in tuberculosis patients.
Methods: A prospective cohort study design was implemented. The sample size was calculated using Epi-info software. Systematic sampling technique was used. Descriptive statistics were used to estimate the micronutrient levels. The general linear model was used to predict the determinants of micronutrient level.
Results: At the start of DOTS (directly observed treatment strategy), 64% of tuberculosis patients had a serum iron level less than 60 μg/dl, 41.9% of tuberculosis patients had serum zinc level less than 52 μg/dl, 29.7% of tuberculosis patients had serum selenium level less than 70 ng/dl, 40.5% of tuberculosis patients had serum vitamin d level less than 20 ng/ml, and 60.4% of tuberculosis patients had urine iodine level of less than 60.4 μg/dl. At the end of the intensive phase, 16.7% of tuberculosis patients had a serum iron level less than 60 μg/dl, <1% of tuberculosis patients had serum zinc level less than 52 μg/dl, <1% of tuberculosis patients had serum selenium level less than 70 ng/dl, 20.4% of tuberculosis patients had serum vitamin d level less than 20 ng/ml, and 53% of tuberculosis patients had urine iodine level of less than 60.4 μg/dl. Serum iron level was affected by HIV infection, hookworm infection, and site of tuberculosis infection: serum vitamin d level was affected by HIV infection: and alcohol dependency affected the serum zinc level of tuberculosis patients during the course of tuberculosis treatments.
Conclusion: Antituberculosis drugs were effective in normalizing the serum zinc and selenium level, but the serum level of iron, vitamin d and iodine were not normalized by the anti-tuberculosis drugs.

Introduction

Micronutrients are commonly referred to as "vitamins and minerals." Micronutrients include minerals such as iron, fluoride, selenium, sodium, iodine, copper and zinc. They also include vitamins such as vitamin C, A, D, E, and K, as well as the B-complex vitamins. Micronutrients deficiency also known as a hidden hunger is common in people living in a developing country [1].

A significant proportion of tuberculosis patient experienced micronutrient deficiency, Anti-tuberculosis drugs especially isoniazid and rifampicin altered the endocrine action of micronutrients [2–13].

Micronutrient deficiency has numerous effects on tuberculosis patients: Micronutrient deficiency increases the risk of respiratory diseases, the risk of depression and anxiety, the risk of mortality, they impair the treatment outcomes, they delay sputum smear conversion, affects response to therapy, they increase the risk of multi-drug resistance (MDR) tuberculosis and activation and progression [5,14–30].

In resource-limited settings like Ethiopia, information regarding the micronutrient level of tuberculosis is not well known. So this

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study will give baseline information to incorporate the issue of micronutrients in the tuberculosis management guideline.

The objectives of this study were to estimate the micronutrients levels of tuberculosis patients during the start of the intensive phase and at the end of the intensive phase (the first 8 weeks of DOTS). The study also aimed to investigate the determinants of micronutrient deficiency among tuberculosis patients.

Methods and materials

A prospective cohort study design was implemented among patients following DOTS in Amhara region. The study was conducted in multi-center health facility. Data were collected from the patients visiting to these health institutions using interview methods. The data were collected from September 2010 to May 2010 Ethiopian calendar targeting tuberculosis patients in the intensive phase. Because of incomplete baseline micronutrient levels, transferred in patients were excluded.

The sample size was calculated using Epi-info software version 7 with the assumption of 95% CI, 80% power, extrapulmonary to pulmonary tuberculosis patient's ratio of 1:1, an odds ratio of 1.5 and 10 nonresponse rate, giving an estimated 448 pulmonary tuberculosis patients and 448 extrapulmonary tuberculosis patients. Systematic random sampling technique was used to select both pulmonary and extra-pulmonary tuberculosis patients.

Initially, baseline data were collected at the start of intensive phase from both pulmonary and extra-pulmonary patients. Then update data were collected at the end of the intensive phase. Interview technique was used to the profile of patients. The blood sample was taken from the patients to measure the serum level of Iron, zinc, iodine, selenium and vitamin D using the standardized operational procedure.

Serum zinc level was measured using atomic absorption spectrophotometer [31], Serum selenium level was measured using atomic absorption spectrometry [32], Serum iron level was measured using cobas6000 (roche kits german) instruments (set 2015; analytics 2014), serum vitamin d level was measured using the mini Vitek Immune Diagnostic Assay System (VIDAS) machine, Urine iodine level was determined using sandell Kolthoff reaction and Concentration technique was used to diagnose hookworm status of the study participants [33]. All laboratory procedures were conducted using strict quality control measures. Alcohol use disorder was measured using CAGE tool [34], Dietary diversification score was measured using WHO recommendations [35].

Completeness of the data was checked at every step. Data were entered into the computer using Epi-info software and transported to SPSS for analysis. Descriptive statistics were used to describe the profile of patients, the baseline and update level of serum micronutrients level. The general linear model (multivariate model) was used to identify the predictors of micronutrient levels.

Ethical clearance was obtained from Bahir Dar University College of medicine and health sciences ethical committee. Support letter was obtained from Amhara national regional state health bureau ethical committee. Written informed consent was obtained from each study participants. The confidentiality of the data was kept at each level. The right to withdraw of study participants at any points was respected. Tuberculosis patients with low micronutrient level were linked to the curative service.

Results

A total of 881 tuberculosis patients were included giving for the response rate of 98%. The mean age of the study participants was 28.5 years (standard deviation [SD] ±14.4 years) (Table 1).

Table 1
The population profile of study participants (n = 881).

SN[a]	Population profile		Frequency	Percentage
1.	Sex	Male	422	47.9
		Female	459	52.1
2.	Residence	Urban	491	55.7
		Rural	390	44.3
3.	Age in years	15–40	763	86.6
		41–65	85	9.6
		>65	33	3.7
4.	Site of infection	Pulmonary tuberculosis	439	49.8
		Extra-pulmonary TB	442	50.2
5.	HIV status	Positive	345	39.2
		Negative	536	60.8
6.	Income in Birr	<2000	695	78.9
		≥2001	186	21.1
7.	Family size	≤4	213	24.2
		>4	668	75.8
	Smoking	Yes	175	19.9
		No	706	80.1
8.	Dietary diversification score (DDS[b])	Poor	483	54.8
		Medium	111	12.6
		High	287	32.6
9.	Hookworm	Infected	250	28.4
		Not infected	631	71.6
10.	Alcohol dependency	Yes	392	44.5
		No	489	55.5
11.	Educational status	Illiterate	170	19.3
		Informal education	179.3	20.3
		Formal education	532	60.4
12.	MUAC[c]	18.0–21.0	143	16.2
		21.1–23.0	353	40.1
		≥23.1	385	43.7

[a] SN = serial number.
[b] Dietary diversification score.
[c] Mid upper arm circumference.

Micronutrient levels of tuberculosis patients at the start of the intensive phase

At the start of DOTS: 64% of tuberculosis patients had a serum iron level less than 60 μg/dl, 41.9% of tuberculosis patients had serum zinc level less than 52 μg/dl, 29.7% of tuberculosis patients had serum selenium level less than 70 ng/dl, 40.5% of tuberculosis patients had serum vitamin d level less than 20 ng/ml, and 60.4% of tuberculosis patients had urine iodine level of less than 60.4 μg/dl (Table 2).

Micronutrient levels of tuberculosis patients at the end of the intensive phase

At the end of the intensive phase, 16.7% of tuberculosis patients had a serum iron level less than 60 μg/dl, <1% of tuberculosis

Table 2
The micronutrient level of tuberculosis patients at the start of intensive phase (n = 881).

SN[a]	Micronutrient	Mean	25 percentiles	50 percentiles	75 percentiles
1	Serum iron level in μg/dl[b]	67.86	46	49	74
2	Serum zinc level in μg/dl	70.63	49	59	98
3	Serum selenium level in ng/dl[c]	95.4	67	97	114
4	Serum vitamin d level in ng/dl	31.81	15	28	47
5	Urine iodine level in μg/dl	92.28	59	95	113

[a] Serial number.
[b] μg/dl = microgram per deciliter.
[c] ng/dl = nanogram per deciliter.

patients had serum zinc level less than 52 μg/dl, <1% of tuberculosis patients had serum selenium level less than 70 ng/dl, 20.4% of tuberculosis patients had serum vitamin d level less than 20 ng/ml, and 53% of tuberculosis patients had urine iodine level of less than 60.4 μg/dl (Table 3).

Predictors of micronutrient change at the end of the intensive phase

After adjusting for HIV infection, dietary diversification score, family size, hookworm infection, alcohol abuse, age, site of tuberculosis infection, MUAC; serum iron level was affected by HIV infection, hookworm infection, and site of tuberculosis infection:, serum vitamin d level was affected by HIV infection: and alcohol dependency affects the serum zinc level of tuberculosis patients during the course of tuberculosis treatments (Table 4).

The serum iron level of HIV positive tuberculosis patients shows a net increment of 14.14 μg/dl at the end of the intensive phase, whereas HIV positive tuberculosis patients resulted for the net increment of 8.12 μg/dl. Hookworm free tuberculosis patients show 18.73 μg/dl additions in the serum iron level, whereas hookworm-infected tuberculosis patients didn't show any increment on the serum iron level. The net increment of serum iron level for the extrapulmonary tuberculosis patients was 9.25 μg/dl, and the net increment of serum iron level for the pulmonary tuberculosis patients was 13 μg/dl. The serum zinc level of tuberculosis patients with alcohol dependency shows a net increment of 9.69 μg/dl, and the net increment of tuberculosis patient free from alcohol dependency shows 44.92 μg/dl (Tables 5 and 6).

Discussion

At the start of DOTS, 64% of tuberculosis patients had a serum iron level less than 60 μg/dl and after the end of the intensive phase, 16.7% of tuberculosis patients had a serum iron level less than 60 μg/dl. The mean serum iron level of tuberculosis patients before they start the intensive phase was 67.86 μg/dl and this figure reached to 84.48 μg/dl at the end of the intensive phase. This finding agrees with finding from Indonesia [36]. Marginal increment of serum iron level was observed during the intensive phase, but this is not adequate increment even at the end of the intensive phase 50% of tuberculosis patients had serum iron level less than 73 μg/dl.

At the start of DOTS, 41.9% of tuberculosis patients had serum zinc level less than 52 μg/dl. At the end of the intensive phase, <1% of tuberculosis patients had serum zinc level less than 52 μg/dl. The mean serum zinc level of tuberculosis patient at the start of the intensive phase was 70.63 52 μg/dl and at the end of the intensive phase this figure reached to 101.03 μg/dl. Satisfactory level of serum zinc response was observed. This finding was in line with finding from Gondar, Ethiopia [19]. This is due to the effect of healing inflammation on zinc metabolism [37].

Table 3
The micronutrient level of tuberculosis patients at the end of intensive phase (n = 881).

SN[a]	Micronutrient	Mean	25%	50%	75%
1	Serum iron level in μg/dl[b]	84.47	63	73	82
2	Serum zinc level in μg/dl	101.03	95	105	106
3	Serum selenium level in ng/dl[c]	109.86	94	114	126
4	Serum vitamin d level in ng/dl	35.29	23	35	47
5	Urine iodine level in μg/dl	115.07	75	95	159

[a] SN=Serial number.
[b] μg/dl = microgram per deciliter.
[c] ng/dl = nanogram per deciliter.

Table 4
Determinants of micronutrient deficiency at the end of the intensive phase (n = 881).

Independent variable	Dependent variable	Mean squire	F	p-value
Smoking	Zinc	151.55	0.67	0.41
	Selenium	908.42	0.70	0.40
	Vitamin D	350.89	0.91	0.34
	Iodine	1698.88	0.83	0.36
	Iron	417.86	2.57	0.11
HIV infection	Zinc	5.52	0.03	0.88
	Selenium	657.68	0.51	0.48
	Vitamin D	1246.58	3.24	0.07
	Iodine	3300.79	1.60	0.21
	Iron	7014.47	43.16	<0.01
Hookworm infection	Zinc	9.06	0.04	0.84
	Selenium	120.02	0.09	0.76
	Vitamin D	0.46	0.001	0.97
	Iodine	2439.08	1.19	0.28
	Iron	38892.01	239.27	0.00
Alcohol dependency	Zinc	169434.42	753.47	0.00
	Selenium	241.39	0.19	0.67
	Vitamin D	79.10	0.21	0.65
	Iodine	283.25	0.14	0.71
	Iron	40.79	0.25	0.62
DDS	Zinc	33.09	0.15	0.86
	Selenium	471.89	0.36	0.70
	Vitamin D	106.98	0.28	0.76
	Iodine	295.16	0.14	0.87
	Iron	252.41	1.55	0.21
Family size	Zinc	53.58	0.24	0.63
	Selenium	65.94	0.05	0.82
	Vitamin D	31.10	0.08	0.78
	Iodine	195.62	0.10	0.76
	Iron	3.32	0.02	0.89
Site of infection	Zinc	389.46	1.73	0.19
	Selenium	184.17	0.14	0.71
	Vitamin D	49.82	0.13	0.72
	Iodine	14.38	0.01	0.93
	Iron	1950.42	12.00	0.00
HIV infection * Site of TB infection	Zinc	46.92	0.21	0.65
	Selenium	3623.83	2.79	0.10
	Vitamin D	549.40	1.43	0.23
	Iodine	519.01	0.25	0.62
	Iron	841.68	5.18	0.02

At the start of DOTS, 29.7% of tuberculosis patients had serum selenium level less than 70 ng/dl. After the end of the intensive phase, <1% of tuberculosis patients had serum selenium level less than 70 ng/dl. The mean serum selenium level of tuberculosis patients at the start of the DOTS was 95.4 ng/dl, at the end of the intensive phase this figure reached to 109.86 ng/dl. The response of serum selenium level during the DOTS regimen was satisfactory. This finding agrees with finding from Iran [38].

At the start of DOTS, 40.5% of tuberculosis patients had serum vitamin d level less than 20 ng/ml. At the end of the intensive phase, 20.4% of tuberculosis patients had serum vitamin d level less than 20 ng/ml. The mean serum vitamin d level of tuberculosis patients at the start of DOTS was 31.81 ng/dl and this figure reached 35.29 ng/dl at the end of the intensive phase. At the end of the intensive phase 50% of tuberculosis patients had a serum vitamin d less than 35 ng/dl. The response of serum vitamin d during the DOTS was not satisfactory. This finding agrees with finding from China [39].

At the start of DOTS, 60.4% of tuberculosis patients had urine iodine level of less than 60.4 μg/dl. At the end of the intensive phase, 53% of tuberculosis patients had urine iodine level less than 60.4 μg/dl. The mean urine iodine level of tuberculosis patients at the start of DOTS was 92.28 μg/dl, and at the end of the intensive phase, the mean urine iodine concentration was at 115.07 μg/dl. The

Table 5
The General linear model outputs for the estimates (n = 881).

Exposure			Mean	95% CI	Outcome
HIV	Negative		14.14	10.65–17.62	Serum iron level at the end of intensive phase – at the beginning of intensive phase
	Positive		8.12	4.64–11.59	
Hookworm	Negative		18.73	15.34–22.11	Serum iron level at the end of intensive phase – at the beginning of intensive phase
	Positive		3.53	−0.08 – 7.14	
Site of infection	Extra pulmonary TB		9.25	5.66–12.84	Serum iron level at the end of intensive phase – at the beginning of intensive phase
	Pulmonary TB		13.00	9.54–16.47	
HIV*site of infection	HIV negative	Extra-pulmonary	13.31	9.64–16.98	Serum iron level at the end of intensive phase – at the beginning of intensive phase
		Pulmonary	14.96	11.26–18.67	
	HIV positive	Extra-pulmonary	5.19	1.22–9.16	
		Pulmonary	11.04	7.39–14.69	
Alcohol dependency	No		44.92	40.73–49.11	Serum zinc level at the end of intensive phase – at the beginning of intensive phase
	Yes		9.69	5.57–13.79	

Table 6
The pairwise comparison of serum micronutrient level for the different predictors (n = 881).

Dependent variable	Independent variable	Mean difference	95% CI for mean difference	p-value
Iron	HIV	6.02	4.22–7.82	<0.01
Iron	Hookworm	15.20	13.27–17.13	<0.01
Iron	Site of infection	−3.75	−5.87–−1.63	<0.01
Zinc	Alcohol dependency	35.24	32.72–37.76	<0.01

iodine intake of tuberculosis patients was not adequate, 50% of tuberculosis patients urine iodine level was less than 95 μg/dl.

Response to the serum iron level of tuberculosis patients was affected by the HIV infection. HIV infection decreases the serum iron response of tuberculosis patients by 6.02 μg/dl. This finding agrees with finding from USA [40]. This might be due to the reasons that blood loss is high among HIV positives due to neoplastic disease (e.g., Kaposi sarcoma in the gastrointestinal tract), decreased RBC production, increased RBC destruction, and ineffective RBC production [41,42].

Hookworm infection decreases the response of serum iron level by 15.2 μg/dl. This finding agrees with finding from Egypt [43]. This is due to the fact that hookworm ingest the red blood cells of the patients [44].

Extra-pulmonary tuberculosis patients show a slow response to serum iron increment than pulmonary tuberculosis patients, the serum iron increment of extra-pulmonary tuberculosis patients were 3.75 μg/dl less than pulmonary tuberculosis patients. This is due to the reason that, in resource-limited settings like Ethiopia extrapulmonary tuberculosis are very difficult to diagnose early and patients were not early detected [45,46].

Alcohol dependency decreases the response of serum zinc level by 35.24 μg/dl. This finding agrees with finding from the united state of America [47]. This is due to the fact that alcohol decreases the absorption of zinc from the gut [48].

Dietary diversification score didn't increase the micronutrient level of tuberculosis patients. This approves that the normal diet is not enough to maintain the serum micronutrient level of tuberculosis patients.

Conclusion

Micronutrient deficiency was a common problem in tuberculosis patients. Anti-tuberculosis drugs were effective in normalizing the serum zinc and selenium level, but the serum level of iron, vitamin d and iodine were not normalized by the anti-tuberculosis drugs.

Recommendation

Micronutrients especially iron, iodine, and vitamin should be supplied for tuberculosis patients. Every tuberculosis patients should be screened and treated for intestinal parasites.

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