http://dx.doi.org/10.17159/2519-0105/2018/v73no8a2

The relationship between oral candidiasis and micronutrient deficiency amongst adult tuberculosis patients in Alexandra, Johannesburg

SADJ September 2018, Vol. 73 No. 8 p489 - p498

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ABSTRACT

Introduction

Tuberculosis (TB), a major public health problem worldwide, is associated with micronutrient deficiency and wasting, and co-infections could worsen the condition.

Aim

To investigate the relationship between micronutrient deficiency and oral candidiasis in adult TB patients.

Methods

A cross-sectional study among 88 TB adult patients in Alexandra, Johannesburg. Patients underwent a complete oral examination to establish the prevalence of candidiasis and blood was collected for the assessment of micronutrient levels.

Results

The mean age of participants was 36.66 years of age, the majority being female (60.23%) and HIV positive (69.30%). The prevalence of oral candidiasis was 39.77% with pseudomembranous being most common (48.00%). In those with micronutrient deficiencies, oral candidiasis was prevalent in 40% patients with Zinc deficiency, 25.00% with Vitamin A deficiency, 32.00% with Albumin deficiency, 33.00% with Selenium deficiency, 31.00% with Iron deficiency and in 36.00% with Vitamin D deficiency.

Conclusion

There was a significant association between the presence of oral candidiasis in TB/HIV co-infected patients and Zinc, Vitamin A and Vitamin D- deficiencies, but not in the TB only group.

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ACRONYMS

CD:	Chronic Diarrhoea
CMV:	Cytomegalovirus
HBV:	Hepatitis B Virus
HCV:	Hepatitis C Virus
HSV-2:	Herpes Simplex Virus - 2
PLWA:	People Living With Aids
TB:	Tuberculosis

Keywords

Tuberculosis, Human Immunodeficiency Virus, Oral Candidiasis, Zinc, Iron , Albumin, Selenium, Vitamin A and Vitamin D micronutrient deficiency

INTRODUCTION

Mycobacterium tuberculosis (*M. tuberculosis*) is the most widespread bacterial pathogen in the world, infecting approximately two million people globally on an annual basis.[1]

Tuberculosis (TB) is a major public health problem in South Africa, with an estimated 450,000 cases of active TB in 2013.[2] The control of TB is complicated by the Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS), with 60.00% of TB patients in South Africa also having HIV.[3]

In South Africa, TB is associated with poverty, overcrowding, alcoholism, stress, drug addiction and malnutrition.[4] An important component of malnutrition is “micronutrient deficiency”, which refers to the lack of sufficient micronutrients in an individual.

Micronutrient deficiency leads to low energy levels, low immunity, higher rates of disability and chronic illness among affected populations.[5]

Those most at risk are children, pregnant and breastfeeding mothers, people living with HIV/AIDS (PLWA) and/or TB.[6] A 2013 report estimated there were 6.1 million people living with HIV in South Africa, with 240,000 South Africans dying annually from AIDS-related illnesses.[7]

These people are particularly vulnerable to extensively drug-resistant tuberculosis because of their increased susceptibility to infection through nosocomial transmission, malabsorption of TB medication, acquired rifampicin resistance and poor response to TB therapy.[8] Patients who have HIV/AIDS, TB and pneumonia are susceptible to opportunistic infections, such as oral candidiasis.[9]

The most common oral candidiasis lesions are pseudo-membranous candidiasis, erythematous candidiasis (oral candidiasis) and angular cheilitis.[10] Micronutrient deficiencies have been reported in individuals with TB[11] and in those with HIV infection alone.[12]

Nutritional deficiencies of Vitamin B12, Zinc and Selenium in malnourished PLWA are associated with decreased immune indices and a higher risk for disease progression.[7]

Oral manifestations of nutritional deficiency include non-specific signs and symptoms that involve the mucous membranes, the teeth, the periodontal tissues, the salivary glands and the perioral skin.[13]

Oral candidiasis is one of the oral lesions strongly associated with manifestations of HIV/AIDS[14]; it is regarded as a marker for immune suppression[15] and for the onset of HIV/AIDS.[16] Oral candidiasis has been reported in 50.00% to 95.00% of all HIV-positive persons at some point during their progression to AIDS.[17]

Opportunistic infections and co-infections that are common among HIV-infected individuals are TB, chronic diarrhoea, oral candidiasis, herpes simplex virus-2 (HSV-2), cytomegalovirus (CMV), hepatitis B virus (HBV) and hepatitis C virus (HCV).

The most common dual infections are chronic diarrhoea (CD) and oral candidiasis, oral candidiasis and TB, CD with TB, HSV-2 and oral candidiasis, HSV-2 and CMV, HBV and HSV-2, HBV and CMV. The least common dual infections are HCV and HBV.

The most common triple infections are oral candidiasis, TB and CD and HSV-2, CMV and CD.[9] Micronutrient deficiencies of Iron, Folic acid, Vit A, B, C, K and Zinc, and a carbohydrate-rich diet have a significant impact on the pathogenesis of oral candidiasis infection.[18]

Paillaud et al.[19] found that oral candidiasis is related to malnutrition and Gupta et al.[20] reported an association between TB and micronutrient deficiency in adults. However, few studies exist that have investigated the association between oral candidiasis and malnutrition in adults with TB.

A comprehensive understanding of the existence of an association between oral candidiasis and malnutrition is important for prevention and for treatment interventions in TB patients.

This study sought to determine the relationship between oral candidiasis and micronutrient deficiency in adults with TB and TB/HIV co-infection, living in Alexandra, Johannesburg.

The objectives were: to determine the prevalence of oral candidiasis amongst TB patients and among TB/HIV co-infected patients; to investigate the association between oral candidiasis and micronutrient status among TB patients and TB/HIV co-infected patients.

MATERIALS AND METHODS

Alexandra, in north eastern Johannesburg, South Africa, has a population of over half a million people living in an area of approximately two square kilometers, with high HIV/AIDS, TB and unemployment rates.[21]

A cross-sectional, analytical study design was adopted for the study, which was part of a large longitudinal study that investigated the impact of a fortified supplementary food on the health and well-being of TB patients. The sample size, therefore, was determined by that larger study.[21]

The inclusion criteria were male and female outpatients, between the ages of 18–60, receiving TB treatment from a clinic in Alexandra. The inclusion criteria also covered a history of at least three regular clinic visits and consent to participate in the study.

The exclusion criteria were: inpatients, outpatients with fewer than three clinical visits, and those receiving treatment for multi-drug resistant TB.[21]

The South African National Tuberculosis Association (SANTA) assisted in identifying Johannesburg clinics in Alexandra that provided TB outpatients with treatment and support. Four Johannesburg clinics were identified and the two with the highest number of TB patients were selected as research sites.

The total sample screened and recruited comprised 120 patients. In only 88 participants was an oral examination carried out and blood specimens collected, as 32 of the recruited participants were not present on the day of examination and blood sample collection.

A questionnaire was designed to establish the demographics and HIV status of the sample population. The oral examination was conducted at the research site by a dentist and a dental therapist, both calibrated.

The patients were seated on mobile dental chairs and examined under headlamp, with disposable hand mirrors being used according to the WHO[21] basic methods recommendations. The inter-examiner agreement was assessed using the kappa statistic, with an overall value of 0.80 – 0.95 for the diagnosis of oral candidiasis.

The diagnosis of the clinical variants of oral candidiasis was made in accordance with the criteria developed by Sharon and Fazel.[22] These criteria characterize pseudo-membranous candidiasis by the presence of extensive white pseudo-membranes consisting of desquamated epithelial cells, fibrin and fungal hyphae.

Erythematous candidiasis is characterized by bright red patches that can be found intraorally; and angular cheilitis is characterized by erythematous fissuring at one or both corners of the mouth and an association with an intraoral candidial infection. Blood samples were collected for serum analysis of the levels of the micronutrients: Selenium, Albumin, Vitamin A, Vitamin D, Iron and Zinc. These data were compared with Alan's normal micronutrient levels.[23]

The relationship between each individual deficient micronutrient and the prevalence of oral candidiasis was analysed to determine if there was a significant association ($p < 0.05$). Within this group of TB patients were patients who were also infected with HIV.

The micronutrient levels were analysed in this TB/HIV sub-group and the data compared with the TB only group. STATA 11 software was used for all statistical analysis. To describe micronutrient levels, the means (standard deviations) and medians (inter-quartile ranges) were used.

Frequencies (percentages) were used to describe categorical variables such as sex, HIV status and employment status. Where comparisons were made, Pearson's Chi-squared test (or Fisher's exact test), the Student t-test or Wilcoxon rank-sum test were used as appropriate. Logistic regression was used to identify factors that were independently associated with a diagnosis of oral candidiasis.

The odds ratios were used to determine the strength of the association. The statistical significance was calculated at the 5% significance level and estimates were reported at the 95% confidence interval.

The Human Ethics Research Committee at the University of the Witwatersrand (M10733), Johannesburg, granted ethics approval. Permission to conduct the study was given by the SANTA and informed written consent was obtained from all participants who volunteered to participate in the study.

RESULTS

The mean age of the total sample (n=88) was 36.66 years (SD. 9.97) with the majority of patients being HIV positive (69.30%). The mean values of the levels of most of the micronutrients (Zinc, Vitamin A, Selenium, Iron, and Albumin) were above the normal ranges.

The exception was Vitamin D, which had a mean level below the normal range (47.96 nmol/L; S.D. 17.91) and 54.90% of the sample recorded a Vitamin D deficiency (Table 1, p491). The mean blood serum level of the micronutrients investigated in the TB/HIV co-infected cases was 69.32% (n=61). The mean values of the levels of all the micronutrients (Zinc, Vitamin A, Selenium, Iron, Albumin and Vitamin D) were above the normal ranges of these micronutrients (Table 2, p491).

In the study sample 39.77% of patients (n=35) had oral candidiasis and 60.22% (n=53) did not have oral candidiasis present. In terms of prevalence of oral candidiasis by clinical type, 48.00% (n=17) of the TB patients had pseudomembranous candidiasis, 28.00% (n=10) had erythematous candidiasis, 14.00% (n=5) had angular cheilitis and 10.00% (n=3) presented a hyperplastic appearance. The prevalence of oral candidiasis was higher among the females (47.17%) than among males (28.57%) and the unemployed subjects had a slightly higher prevalence of oral candidiasis (41.53%) than did those employed (34.78%).

Forty one per cent of TB/HIV co-infected patients presented with oral candidiasis compared with 7.03% of TB patients (p=0.754). There was no statistically significant relationship between oral candidiasis and any of the demographics (Table 3, p493). For subjects with oral candidiasis, micronutrient levels below the normal range were present among 40% of patients for Zinc, 26% for Vitamin A, 33% for Selenium, 32% for Iron, 32% for Albumin and 33% of the sample for Vitamin D.

For TB patients with oral candidiasis, micronutrient levels within the normal range were present among 23.00 % for Zinc, 47.00% for Vitamin A, 24.00% for Selenium, 39.00% for Iron, 30.00% for Albumin and 17.00% for Vitamin D.

Oral candidiasis was not significantly associated with lower levels of micronutrients when compared with normal micronutrient levels in TB patients who had no oral candidiasis (Table 4, p493).

No significant association existed between the demographic variables or the micronutrient levels and the presence of oral candidiasis in TB patients (Table 5, p495). Sex [OR:0.61(95% CI:0.24-1.52)], Employment status [OR:1.13 (95% CI: 0.42-3.09)], HIV status [OR: 1.12(95% CI : 0.44-3.44)], Micronutrient level of Zinc [OR:2.25 (95% CI: 0.61-8.25)], Vitamin A [OR:0.37 (95% CI: 0.13-1.07)] , Selenium [OR: 11.41 (95% CI 0.12-17.11)] , Iron [OR: 0.75 (95% CI: 0.27-2.03)] , Albumin [OR:10.82 (95% CI: 0.28-2.41)] and Vitamin D [OR: 2.25 (95% CI: 0.61-8.25)].

However, in patients with TB/HIV co-infection there was a significant association between the presence of oral candidiasis and deficiencies in the levels of Zinc [OR: 2.25 (95% CI: 1.9-2.4)], Vitamin A [OR: 1.5 (95% CI: 1.2-1.8)] and Vitamin D [OR: 2.63 (95% CI: 2.45-3.00)] (Table 6, p495).

DISCUSSION

This study sought to investigate the relationship between oral candidiasis and micronutrient deficiencies in adults with TB and with TB/HIV co-infection. The majority of the study participants were females (60.23%) and unemployed (73, 90%).

The higher percentage of females might simply be because more females have TB or are co-infected with TB and HIV[3] but may be more likely to be compliant in attending clinics for TB treatment and recall visits than males.[24] Also, Brennan et al.[25] reported that females tend to make use of public health services more often than males.

Although 69.32% of the TB patients in the current study were HIV positive, John et al.[26] reported a 90% rate of TB/HIV co-infection amongst patients admitted to the Medical Ward in Helen Joseph Hospital in Johannesburg. This level of co-infection is significantly higher than the prevalence

Table 1: Individual micronutrient deficiency of TB patients (n=88)

Micronutrients	n	%	Median(IQR)	Mean (Std Deviation)
Zinc n = 49				
No (> 8.2 µmol/L)	34	69.39	10.05 (7.40 – 11.10)	10.60 (4.66)
Yes (< 8.2 µmol/L)	15	30.61		
Vit A n = 65				
No (> 1.05 µmol/L)	34	52.31	1.05 (0.74 – 1.46	1.13 (0.43)
Yes (< 1.05 µmol/L)	31	47.69		
Selenium n = 44				
No (> 46 µg/L)	41	93.18	68.00 (58.00 – 83.00)	69.12 (17.41)
Yes (< 46 µg/L)	3	6.82		
Iron n = 67				
No (> 9 µmol/L)	36	53.73	10.10 (6.60 – 15.80)	11.19 (6.59)
Yes (< 9 µmol/L)	31	46.27		
Albumin n= 67				
No (> 35 g/L)	46	68.66	38.00 (33.00 – 41.00)	37.28 (5.55)
Yes (< 35 g/L)	21	31.34		
Vit D n= 51				
No (>49 nmol/L)	23	45.10	46.35 (36.13 – 60.23)	47.96 (17.91)
Yes (< 49 nmol/L)	28	54.90		

Table 2: Individual micronutrient deficiency of TB/HIV co-infected patients (n=61)

Micronutrients	N	%	Median(IQR)	Mean (Std Deviation)
Zinc n = 35				
No (> 8.2 µmol/L)	15	43.00	10.00 (6.20– 11.00)	9.60 (5.82)
Yes (< 8.2 µmol/L)	20	57.00		
Vit A n = 28				
No (> 1.05 µmol/L)	17	60.71	1.00 (0.82 – 1.32)	1.08 (0.68)
Yes (< 1.05 µmol/L)	11	39.28		
Selenium n = 36				
No (> 46 µg/L)	23	64.00	62.00 (55.00-73.00)	67.15 (13.28)
Yes (< 46 µg/L)	13	36 .00		
Iron n = 36				
No (> 9 µmol/L)	15	41.66	9.63 (7.80 – 13.80)	10.60 (7.20)
Yes (< 9 µmol/L)	21	58.00		
Albumin n= 37				
No (> 35 g/L)	23	62.00	39.00 (31.00-39.00)	38.42 (4.62)
Yes (< 35 g/L)	14	38.00		
Vit D n= 46				
No (> 49 nmol/L)	17	37.00	44.28 (34.22 – 61.48)	49.46 (19.84)
L (< 49 nmol/L)	29	63.00		

rates reported in other parts of the world such as 18. % in Zimbabwe,[27] 19.80% in Nigeria,[28] 17% in India[29] and less than 30% in Europe.[30] The link between TB and malnutrition consists of two interactions: the effect of TB upon the nutritional state and, the effect of malnutrition on the occurrence and clinical manifestations of the disease.[2,31]

In TB cases, nutrients (e.g. Iron, Copper, Selenium and Zinc) are compartmentalised to the tissues, lost from the body and/or blocked from cellular utilization.[32] Approximately forty per cent (n=35) of the TB patients in this study had oral candidiasis, with pseudomembranous oral candidiasis being overall the most prevalent (48.00%), more prevalent in females and in those above the mean age of 37, but the differences were not significant.

Ikebe et al.[33] also reported that candidal activity was not significantly associated with age or sex in relatively healthy individuals of above 60 years of age, as certain systemic conditions (e.g. diabetes mellitus), defects of the immune system 34-36, and some medications (e.g. antibiotics, corticosteroids) may predispose towards the transformation of colonisation of species such as Candida into opportunistic pathogens.[37]

In addition, oral candidiasis was more prevalent in HIV-positive (40.98%) patients than in HIV-negative patients, although the difference was not significant. This finding is in line with the findings of Akpan et al.[38] who reported that 95.00% of HIV-positive individuals in their study had oral candidiasis. In the majority of HIV-positive patients, oral candidiasis is often present as an initial manifestation of HIV infection,[16] and is a useful clinical marker of patients with high viral load.[39]

Even though only 40.98% of the HIV-positive cases in the current study had oral candidiasis, evidence has shown that oral candidiasis is one of the key opportunistic infections that occur commonly and that it frequently presents in HIV-positive cases.[14,15] The oral cavity is a reservoir of different potential pathogens – bacterial, viral and fungal – which can multiply and cause disease in malnourished and immunocompromised patients.

Samaranayake et al.[18] reviewed the literature and contend that only a few studies have investigated nutrient factors such as Zinc, Albumin, Selenium, Iron, Vitamins A and D and their possible role in the alteration of oral mucosal integrity.

In this study, 30.61% of the sample had Zinc deficiency; this prevalence was significantly lower than that reported by Koyanagi et al[40] in their study of 56 TB patients, 61.00% of whom had Zinc deficiency. A study investigating the relationship between wasting and micronutrient malnutrition conducted by van Lettow et al.[41] also reported that TB patients (n=801) were at a higher risk of Zinc deficiency with a prevalence as high as 85.00%.

Tuberculosis/HIV co-infection worsens Zinc deficiency in patients; in the current study 57.00% of the TB/HIV co-infected patients had Zinc deficiency. Studies have also shown Zinc deficiency to be more prevalent in TB/HIV co-infected cases versus TB only controls.[41,42] In the present study, 40.00% of the TB patients had oral candidiasis and Zinc deficiency and 23.00% had oral candidiasis associated with Zinc levels in the normal range. However, there was no significant relationship between oral candidiasis and Zinc deficiency. In contrast, Paillaud et al.[19] reported a significant association between oral candidiasis and Zinc deficiency (44.00%; p=0.031].

An estimated 69.32% of the current sample were co-infected with TB/HIV and Baum et al.[43] reported Zinc deficiency in 56.00% of HIV-positive drug users (n=118). It is important to note that Zinc deficiency has been linked to a declining CD4 count in HIV-positive individuals because in that status the generation of T cells is reduced and humoral and cell-mediated immunity are depressed; thus, Zinc supplements are important in Zinc-deficient HIV/AIDS patients even among those being administered HAART.[44] Unfortunately, in our study this analysis was not possible because of the number of CD4 count records that were unavailable. There was Iron deficiency in 46.27% of our TB patients, of whom 58.00% were from the TB/HIV co-infected patients, with no significant association between Iron deficiency and TB or TB/HIV co-infection.

This finding is in contrast to the findings reported by Kassu et al.[42] who found that there was a significant difference in Iron deficiency between TB/HIV co-infected patients (n=74) and healthy controls (n=31) ($p<0.05$). There was also Iron deficiency in the TB patients without HIV co-infection versus healthy controls, but the difference was not statistically significant ($p < 0.07$). Taha and Thanoon[45] also reported that serum Iron values were significantly lower in pulmonary TB cases (n=40) in comparison with controls (n=50; $p <0.001$).

Although the current study did not find a significant association between Iron deficiency and TB-only infected cases and TB/HIV co-infected cases, studies have shown that severe Iron deficiency in TB/HIV co-infected cases is directly linked to HIV infection, as HIV-positive cases experience reduction in food intake[32] and malabsorption of nutrients,[46] making patients co-infected with TB/HIV more vulnerable to Iron deficiency.

Oral candidiasis was present in patients both with Iron deficiency and those with Iron levels within the normal range. There was no significant difference between those with high Iron and oral candidiasis compared with those with low Iron levels. Neither could Walker et al.[47] find any differences in the frequency of oral candidiasis or oral carriage rate of Candida in Iron-deficient subjects and controls, nor there a significant change in the disease process observed after Iron replacement therapy.

Similarly, Samaranayake[18] identified five Iron-deficient patients with chronic atrophic oral candidiasis in whom adequate restoration of serum Iron levels had no effect on the recurrence of oral candidiasis. In addition, Jenkins et al.[48] could not establish a relationship between Iron deficiency and chronic atrophic or hyperplasic variety of oral candidiasis. Recurrent oral candidiasis infection in normal Iron levels could be the result of diseases, such as diabetes mellitus and dentures. Paillaud et al.[19] reported a high prevalence of oral candidiasis in hospitalised patients above 70 years of age who were Iron-deficient and also had angular cheilitis and atrophic glossitis. The difference

Table 3: Associations between oral candidiasis and demographics (n=88)

Demographics	No oral candidiasis (n=53)		Oral candidiasis Present (n=35)		*p value
Age in years Median(IQR) Mean (Std Deviation)	35.50 (28.00 – 42.00) 36.50 (10.21)		38.00 (31.00 – 44.00) 37.35 (9.47)		0.702
Demographic Variables	**n**	**%**	**n**	**%**	
Female	28	52.83	25	47.17	0.305
Male	25	71.43	10	28.57	
Unemployed	38	58.46	27	41.53	0.852
Employed	15	65.22	8	34.78	
HIV Negative (TB positive)	17	62.96	10	37.03	0.754
HIV Positive (TB/HIV co-Infection)	36	59.01	25	40.98	

*p value for Student's t test for normally distributed continuous variables (e.g. Age), Wilcoxon rank-sum test for non-normal continuous variables and Pearson's Chi squared test for categorical variables, Fisher's exact test for categorical variables with n < 5 per cell.

Table 4: Associations between oral candidiasis and micronutrient deficiency amongst TB/HIV co-infected patients (n=61)

Micronutrient Deficiency	No Oral Candidiasis		Oral candidiasis Present		*p value
Zinc n=49	**N**	**%**	**N**	**%**	
No (> 8.2 µmol/L)	26	77.00	8	23.00	0.216
Yes (< 8.2 µmol/L)	9	60.00	6	40.00	
Median (IQR)	10.05 (8.20-11.10)		9.60 (6.80-12.90)		0.705
Mean (Std Deviation)	10.33 (3.25)		11.30 (7.24)		
Vitamin A n=65					
No (> 1.05 µmol/L)	18	53.00	16	47.00	
Yes(< 1.05 µmol/L)	23	74.00	8	26.00	0.063
Median (IQR)	0.99 (0.69-1.32)		1.21 (0.99-1.58)		0.182
Mean (Std Deviation)	1.07 (0.45)		1.22 (0.39)		
Selenium n=44					
No (> 46 µg/L)	31	76.00	10	24.00	
Yes (< 46 µg/L)	2	67.00	1	33.00	1.000
Median (IQR)	68.00 (58.00-83.00)		65.00 (58.50-78.50)		0.739
Mean (Std Deviation)	69.65 (17.94)		67.67 (16.57)		
Iron Deficiency n=67					
No (> 9 µmol/L)	22	61.00	14	39.00	
Yes (< 9 µmol/L)	21	69.00	10	32.00	0.567
Median (IQR)	9.5 (6.90-15.20)		10.10(6.05-17.00)		0.816
Mean(Std Deviation)	11.33 (6.96)		10.94(5.98)		
Albumin n=67					
No (> 35 g/L)	32	70.00	14	30.00	0.728
Yes (< 35 g/L)	14	67.00	7	33.00	
Median (IQR)	37.00 (34.00-41.00)		39 (31.50-40.50)		0.978
Mean (Std Deviation)	37.29 (5.69)		37.25 (5.37)		
Vitamin D					
No (> 49 nmol/L)	19	83.00	4	17.00	0.210
Yes (< 49 nmol/L)	18	64.00	10	36.00	
Median (IQR)	48.83 (36.13-60.23)		43.39 (35.81-64.58)		0.739
Mean (Std Deviation)	48.45 (17.47)		46.57 (19.67)		

*p value for Wilcoxon rank-sum test for non-normal continuous variables and Pearson's Chi squared test for categorical variables, Fisher's exact test for categorical variables with n < 5 per cell.

in the findings may be the result of the difference in the demographics of the population (age and hospitalised) and the study design.

Also institutionalisation may render elderly individuals vulnerable to nutritional deficiency[49,50] because the storage of foods and the cooking procedures used in institutions may contribute to the loss of vitamins from the food.

Hospitalised elderly TB patients also have limited food choice, which ultimately affects their food intake and micronutrient serum levels as compared with TB outpatients. There is also a high prevalence of edentulousness in elderly patients, which limits their food choice and impacts negatively on their micronutrient status[51] as compared with the TB dentate sample (100% of the population had more than 20 teeth in their mouths).

Also none of the sample for the current study had dentures while the sample used in Sheiham's[51] study had dentures. Dentures and old age are a high risk for oral candidiasis, which probably explains findings of Paillaud et al.[19]

In this study, 48.00% of the sample had Vitamin A deficiency; this result compares closely with Koyanagi et al.[40], who showed that there was a significantly lower mean Vitamin A presence in the TB cases compared with the non-TB controls.

However, Karyadi et al.[11] in a randomised control trial investigating whether Vitamin A- and Zinc supplementation increased the efficacy of anti-tuberculosis treatment with respect to clinical response and nutritional status, reported that at baseline 32.00% of newly diagnosed TB patients (n=80) had Vitamin A deficiency.

The lower percentage of Vitamin A deficiency in Karyadi et al.'s[11] study is probably because the sample consisted of newly diagnosed TB patients who had never received any anti-TB intervention. In our study, Vitamin A deficiency was seen in 60.71% of the TB/HIV co-infected patients as compared with 47.69% of the TB-only infected patients. The high proportion of individuals with low Vitamin A levels in the TB/HIV co-infected subgroup cannot be explained by nutritional deficiencies alone.

Studies have also shown that low Vitamin A levels are common in patients with TB and in those infected with HIV and are even more severe among patients with HIV/TB co-infection.[12]

Mugusi et al.[52] reported that serum Vitamin A levels were lower among HIV-infected individuals and lowest among TB/HIV co-infected patients. Low levels of Vitamin A were found to be more common among TB patients with a significantly higher prevalence among the HIV positive (64, 40%) than in healthy controls (9.10%).[48]

Although the current study did not show any significant association between Vitamin A deficiency and TB or TB/HIV co-infected subgroups, it seems that TB/HIV co-infection may potentially worsen Vitamin A deficiency more than TB or HIV alone because Vitamin A deficiency is associated with TB/HIV co-infection and more pronounced with HIV disease progression.[43]

Approximately 7.00% of the TB patients in this study had Selenium deficiency. Koyanagi et al.[40] reported a significantly lower Selenium concentration in pulmonary TB cases in Ecuador than in the healthy controls. Koyanagi et al.[40] also reported that only 6.52% HIV/TB cases had Selenium deficiency, whereas our study found that of the 69.32% of the sample who had TB/HIV co-infected cases, 33.00% had Selenium deficiency.

An inverse correlation between Selenium and HIV infection was reported by Dworkin,[53] as plasma Selenium in AIDS patients was found to be significantly lower in AIDS cases than in the healthy controls. Patients with AIDS had more severe Selenium deficiency compared with those with earlier stages of HIV infection. The current study and other reported studies indicate that those with TB/HIV co-infection are susceptible to lower concentrations of Selenium as compared with TB-only infected cases or healthy controls (non-TB).

Furthermore, Kassu et al.[42] reported that the mean serum level of Selenium was significantly lower in pregnant women with HIV co-infection compared with HIV-negative pregnant women. Oral candidiasis was present in patients with Selenium deficiency (33.00%) and in patients with Selenium levels within the normal range (24.00%), with no significant difference between oral candidiasis levels and Selenium levels. Whilst the current study did not analyse the viral loads in the TB/HIV co-infected cases, Dworkin[53] reported significantly lower Selenium levels in AIDS cases than in controls.

Selenium deficiency is common in HIV-positive- and AIDS patients. AIDS patients tend to have more severe deficits than those with earlier stages of HIV infection.[47] Albumin deficiency was found in 31.34 % of the TB cases, and in 38.00% of the TB/HIV co-infected cases, with no statistically significant association. However, Ramakrishnan et al.[54] reported significantly lower serum levels of Albumin in TB/HIV co-infected cases than in TB cases.

Mugusi et al.[48] also reported that the mean serum Albumin was significantly lower in HIV-positive patients; however, when Okamura et al.[55] further investigated the relationship between hypoalbuminemia and computed tomography studies of the lungs, the finding was reported that hypoalbuminemia was significantly related to the presence of typical radiographic evidence of TB in patients of over 70 years of age. Fifty-five per cent of the TB patients in the current study had Vitamin D deficiency; however, a case control study by Ho-Pham et al.[56] reported that the prevalence of Vitamin D insufficiency was 35.40% in men with TB and 19.50% in controls (p = 0.01). In women, there were no significant differences in Vitamin D levels between TB patients and controls.

The prevalence of Vitamin D insufficiency in women with TB (45.30%) was not significantly different from those without TB [p=0.91). Nansera et al.'s[57] study, which measured Vitamin D and calcium levels in HIV-negative-, HIV-infected- and TB/HIV co-infected adults, also reported individuals with TB/HIV co-infection were usually suffering from severe micronutrient malnutrition due to a combination of TB infection and high viral load. In the present study, oral candidiasis was present in patients with micronutrient

Table 5: The odds ratio between demographics, micronutrient levels and Oral Candidiasis (n=88)

Demographics	Odds Ratio	95% Confidence Interval	*p value
Age in years	1.01	0.97 – 1.05	0.698
Sex Female Male	 1 0.61	 0.24 – 1.52	 0.284
Employment No Yes	 1 1.13	 0.42 – 3.09	 0.804
HIV Status Negative Positive	 1 1.12	 0.44 – 3.44	 0.845
Zinc Deficiency No (> 8.2 µmol/L) Yes (< 8.2 µmol/L)	 1 2.25	 0.61 – 8.25	 0.221
Vitamin A Deficiency No (> 1.05 µmol/L) Yes (< 1.05 µmol/L)	 1 0.37	 0.13 – 1.07	 0.066
Selenium Deficiency No (> 46 µg/L) Yes (< 46 µg/L)	 1 11.41	 0.12 – 17.11	 0.788
Iron Deficiency No (> 9 µmol/L) Yes (< 9 µmol/L)	 1 0.75	 0.27 – 2.03	 0.567
Albumin Deficiency No (> 35 g/L) Yes (< 35 g/L)	 1 10.82	 0.28 – 2.41	 0.724
Vitamin D Deficiency No (> 49 nmol/L) Yes (< 49 nmol/L)	 1 2.25	 0.61 – 8.25	 0.221

Table 6: The odds ratio between micronutrient deficiency and Oral Candidiasis in TB/HIV co-infected (n=61)

Micronutrient levels	Odds Ratio	95% Confidence Interval	*p value
Zinc No (>8.2µmol/L) Yes (< 8.2 µmol/L)	 1 2.25	1.90 -2.40	0.021
Vitamin A (> 1.05 µmol/L) (< 1.05 µmol/L)	1 1.50	1.20 -1.80	0.020
Selenium No (> 46 µg/L) Yes (< 46 µg/L)	 1 1.40	 0.95 -1.50	 1.003
Iron No (> 9 µmol/L) Yes (< 9 µmol/L)	 1 0.75	 0.55 -1.20	 0.570
Albumin No (< 35 g/L) Yes (< 35 g/L)	 1 0.80	 0.45 -1.30	 0.732
Vitamin D No (> 49 nmol/L) Yes (< 49 nmol/L)	 1 2.63	 2.45 -3.00	 0.022

deficiency and in patients with micronutrient levels within the normal range. Few studies have investigated the relationship between these micronutrients (Vitamin A, Albumin and Vitamin D) and oral candidiasis in TB patients. However, Steenkamp et al.[58] reported a deficiency in micronutrients such as Albumin, Vitamin A and Vitamin D.

Steenkamp et al.[58] also indicated the negative impact HIV and high viral load have on these micronutrient deficiencies, and oral candidiasis has been identified as one of the oral lesions strongly associated with HIV/AIDS[14] and as a marker of immune suppression.[50]

Other different host factors are independently implicated in the development of oral candidiasis. These include old age, treatment with antibiotics, denture wearing and neglected oral hygiene, all of which predispose patients to the occurrence of oral candidiasis.[51]

LIMITATIONS

This study had a few limitations worth highlighting. One was the small sample size of TB patients and another the lack of a control group. These two limitations restricted the ability to draw conclusions about the associations between the independent and dependent variables.

Another limitation was reliance on the self-reported HIV status, necessary as budgetary constraints precluded comprehensive diagnostic testing. However, the self-reported HIV positive status was above the national average[61] and this is not surprising in the resource-poor setting of Alexandra and the context of widespread co-infection with HIV and TB in South Africa.[21]Future studies would benefit from much larger sample sizes to draw more convincing conclusions.

This study is, however, a useful starting point for understanding the association between micronutrient deficiency and oral candidiasis in TB patients. More case control studies are needed to investigate the association of micronutrient deficiency and oral candidiasis in TB cases versus non-TB cases.

CONCLUSION

The present study shows a high prevalence of oral candidiasis, especially pseudomembranous oral candidiasis, as well as a high prevalence of several micronutrient deficiencies among adult TB patients.

There was a significant association between the presence of oral candidiasis in TB/HIV co-infected patients and Zinc-, Vitamin A- and Vitamin D- deficiencies. The present findings underline the importance of an oral examination and the need for mineral and vitamin supplements in adult TB patients, especially those who are TB/HIV co-infected.

Acknowledgements

Research Partners

Siyakhana Initiative for Ecological Health and Food Security, Wits Health Consortium
South African National Tuberculosis Association (SANTA)
City of Johannesburg, Department of Health and Housing
Edmore Miranda, Mazvita Senganyi

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