Micronutrient Deficiency and Tuberculosis

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"Bwe medikaman san manje, se lave men, siye até." Haitian expression
("To give medication without food, is to wash your hands and dry them in the dirt.")

A. Study Purpose and Rationale

Tuberculosis remains a significant public health problem throughout the world. 1.7 billion people or approximately one third of the world's population are infected with *Mycobacterium tuberculosis*.[1] During the 1990s, an estimated 30 million people died as a result of TB, resulting in the observation that TB may be the most important pathogen in the world today.[2] HIV has added synergistically to the scourge of tuberculosis, with rates of HIV associated TB increasing dramatically in the late 1980s and early 1990s. In addition, poor adherence, dismantling of the public health infrastructure, inadequate supervision of TB medication administration, had resulted in significant rates of multidrug resistant TB in cities in the US, such as NYC, and also throughout the world, most prominent in Russia (>20% in the prison system)[3] and the Dominican Republic[4].

In the days when the sanitarium was the only treatment for tuberculosis, a great deal of emphasis was placed on nutrition, nutritional supplementation (cod liver oil,) and sunlight and fresh air. Since the discovery of streptomycin and subsequent development of effective anti-tuberculosis therapy, the role of nutrients, whether macro or micronutrients have fallen rather by the wayside in the discussion of susceptibility and/or treatment of tuberculosis. However, the two key developments of HIV and MDR=TB in the past two decades suggest that the role of nutrition perhaps should not be so easily brushed aside. Tuberculosis, the original phthisis has found a new co-conspirator in HIV and there is much evidence of the synergistic effect of TB in HIV wasting. In addition, the development of multidrug resistance tuberculosis leads some to speculate that chronic disease may become more prevalent. Thus, it will be even more necessary to understand the role of nutrition in activation of tuberculosis.[5]

Malnutrition has been observed in patients with tuberculosis since the time of Hippocrates. Several more recent studies demonstrate patients with active pulmonary tuberculosis are malnourished as indicated by measurements of macronutrient nourishment status, i.e. reductions in visceral proteins and anthropometric indexes. Onwuballi found that patients in Harrow, England with active tuberculosis had significant reductions in BMI, triceps skinfold thickness, arm muscle circumference, serum albumin, iron, TIBC and that chemotherapy was associated with nutritional recovery and restoration of nutrition related indices. [6] Saha et al demonstrated severe weight loss, reduction of skinfold thickness, decreased albumin, prealbumin and retinol binding protein, zinc and calcium levels in tuberculosis patients in Delhi, India [7]. Tsukaguchi et al also described malnutrition in patients with tuberculosis in Japan. [8]

However, fewer studies document specific micronutrient deficiencies in patients with tuberculosis. Vitamin A deficiency was found to be common in adults with TB and HIV in Rwanda.[9] Deficiency of vitamin A has been implicated in several studies t be associated with decreased immune function. Vitamin A deficiency has been demonstrated to increase bacterial adherence to respiratory epithelial cells.[10] Retinoic acid can inhibit the multiplication of mycobacterium in macrophages.[11] Requirement of vitamin A during infection increases due to increased rate of excretion and metabolism. [12] These studies suggest that vitamin A has an immunoprotective role against tuberculosis. This observation has a basis in historical fact as cod liver oil, rich in vitamins A and D was used regularly for the treatment of tuberculosis prior to the discovery of effective chemotherapy. [13]

Zinc is essential in mobilizing vitamin A from the liver.[14] In addition, zinc deficiency also affects immune defense. In animal models, it has been demonstrated to result in decreased phagocytosis, reduced numbers of circulating T cells, and reduced PPD reactivity.[15] Zinc deficiency has been reported in patients

with tuberculosis in both China and India.[16] Chemotherapy with antituberculosis drugs increased zinc concentrations in childhood tuberculosis patients in India, resulting in the suggestion that perhaps zinc status is a marker for monitoring the severity of disease and response to therapy. [17] In addition, zinc supplementation of patients with pulmonary tuberculosis and bacterial pneumonia was shown to increase immune function.[18]

Two seminal studies in this field were done by Karyadi et al in Indonesia. The first study was a case-control study conducted in Jakarta, Indonesia that demonstrated that patients had significantly lower BMI, skinfold thicknesses, upper arm circumference, proportion of fat, concentrations of albumin, hemoglobin, retinal and zinc. Karyadi et al found that the proportions of patients with tuberculosis and control subjects with vitamin A deficiency were 33% and 13% respectively. The proportions of zinc deficiency among tuberculosis patients and control subjects were 21% and 5% respectively.[19]

A double-blind, placebo controlled trial was done to follow up the case control study and see if vitamin A and zinc supplementation affect clinical response and nutritional status in patients with tuberculosis receiving anti-TB therapy. They looked at 40 patients each, one group received anti-TB meds with 5000 IU of vitamin A and 15 mg of zinc (recommended USDA) while the other group received standard anti-TB therapy. All patients received clinical exams, assessments of micronutrient status, and anthropometric measurements before and after 2 and 6 months of therapy. They found that at baseline 64% had BMI<18.5, 32% had vitamin A deficiency and 30% had zinc deficiency. After treatment, zinc levels were not significantly different between groups. After 6 months of treatment, vitamin A levels were significantly higher in the micronutrient group. In addition, they showed that sputum conversion and resolution of X-ray area occurred earlier in the micronutrient group.[20] Thus, they concluded that vitamin A and zinc supplementation improves the effect of tuberculosis medication after 2 months of treatment and results in earlier sputum conversion.

B. Study Design and Statistical Analysis

I propose to conduct two studies to answer the following questions:

- What is the role of micronutrient (vitamin A and zinc) deficiency in susceptibility to tuberculosis infection?
- What is the role of micronutrient supplementation in the efficacy of tuberculosis treatment?

The initial will be a cross sectional case- control study (1) and the second will be a double-blinded placebo controlled clinical trial (2).

Study (1) will enroll all adult TB patients identified at DOH at 168th/Broadway as cases and their PPD+ friends and family as controls. (1) The parameters assessed will be vitamin A and zinc deficiency at initial diagnosis of TB and PPD+ status. Chi square tests will be used to compare the proportions of those cases with deficiency with controls with deficiency. Based on estimates from the Indonesian case control study and the following sample size calculation which uses 80% power calculation and $p<0.05$:

(e.g. for zinc p_1=21% with deficiency, q_1=79%, p_2=10% and q_2=90% and for vitamin A p_1=33% with deficiency, q_1=67% and p_2=13% and q_2=87%)

$$\mathbf{n= 8\ ((p_1q_1 + p_2q_2)/effect^2) +2/effect +2}$$

where $\mathbf{p_1, p_2}$ **are** the proportions of vitamin deficiency in cases and controls

$\mathbf{q=1-p}$

$$\mathbf{effect\ is\ |p_1 - p_2|}$$

n=80 for the zinc group and n=78 for the vitamin A group. Thus, 100 subjects will be enrolled for each arm.

For study (2) the double blinded, placebo controlled randomized clinical trial; all TB patients at DOH will be enrolled. They will be randomized by an automated clinical response system (i.e. pharmacist will call an automated clinical response system, receive notification as to whether the person is to be placed in the micronutrient or placebo group.) Both groups will receive standard TB therapy as determined to be appropriate by their physicians. In addition, the micronutrient group will receive 5000

IU of vitamin A and 15 mg of zinc. The placebo group will receive two identical pills containing lactose or sucrose. The number of patients required for reduction in mean lesion size is calculated with the following unpaired t-test calculation, which approximates n using 80% power and $p<0.05$. (std-devn=+/- 13 cm^2 and effect=30 cm^2)

$$\mathbf{n = 1+ 16(std\text{-}devn/effect)^2}$$

std-dvn= outcome measure across subjects

effect= postulated group difference in outcome measure.

N<6 patients.

The number of patients required for the sputum smear conversion is calculated by the chi square sample size test (as above) and results in n=219. Thus 250 patients will be enrolled for the RCT. There will be no cross over in this study.

C. Study Procedure

The study procedure for study (1) will involve drawing an extra 15 ml of blood, which is minimally invasive and should not result in any extra pain, discomfort or inconvenience as it can be done along with routine blood draws required at the initial visit at DOH. Cases and controls will be consented, have two tubes of blood drawn, and their involvement with the study will be over. For study (2), the patients will be given 2 additional pills, vitamin A and zinc, or two additional placebo pills which they will have to take in addition to their chemotherapy against tuberculosis. They will have CXRs done at 2 months and 6 months, which shall be no different than routine CXRs done during clinical treatment and evaluation for tuberculosis. In addition, they will be interviewed by the study research nurse using a standard health questionnaire that will be similar to their DOH evaluation but will include additional questions regarding vitamin supplements taken, nutritional practices, and a 24-hour food recall. Duration of the participants' involvement is expected to be 6 months, the expected duration of treatment.

D. Study drugs

For study (2) the study "drugs" are vitamin A 5000 IU and zinc 15 mg, which shall be administered orally with antituberculosis medications. The dosage regimen is identical to the USDA. No side effects are expected.

E. Medical device

No medical device will be used in this study.

F. Study questionnaires

The study questionnaires used in study will be a standard H+P with a few additional questions regarding vitamin supplementation, nutritional practices, and a 24-hour food recall. The questionnaires will be available in English and Spanish and will be administered by bilingual personnel. They are currently under development and will be submitted when available.

G. Study Subjects

For study (1) all patients with active pulmonary tuberculosis will be identified at DOH and asked to participate. Their PPD+ contacts will be asked to participate as controls.

For study (2) all patients with active pulmonary tuberculosis will be identified at DOH and asked to participate.

Patients will be excluded from both studies if they have any malignancy, are HIV positive, and/or any other debilitating condition other than tuberculosis.

Vulnerable populations such as minors, mental patients, prisoners, institutionalized persons will not be included. Pregnant women, elderly persons, and members of ethnic minorities will not be excluded. They are to be included as this study specifically is interested in treating vulnerable patients with tuberculosis and by including vulnerable patients, it will be possible to study exactly those patients that will benefit most greatly from this study.

H. Recruitment of Subjects

The patients will be recruited when they present to DOH with active tuberculosis and their contacts are identified for studies (1) and (2). Patients will be asked to participate by their DOH physician.

I. Confidentiality of Study Data

The study data will be coded. Data will be stored in a secure location off CPMC campus accessible only to the primary investigator.

J. Potential Conflict of Interest

There is no potential conflict of interest in this study. Neither the principal investigator nor the University has a proprietary interest in vitamin A and/or zinc. Nor do either party stand to benefit financially in any way from the results of the investigation.

K. Location of the Study

Study (1) will take place at DOH and/or CPMC Pulmonary Clinic location. Study 2 will take place at DOH as well. It is possible that study 2 may be conducted Clinique Bon Saveur in Cange, Haiti. If this is done, all study materials will be translated into French Creole.

L. Potential Risks

There are no potential risks associated with the study other than the minor discomfort of a blood draw.

M. Potential Benefits

For study (1) the phrase "You may or may not benefit as a result of your participation" will be included in the consent form and verbal consent discussion. The subjects will be informed that the potential benefit of study (1) is documenting an association with vitamin A deficiency and zinc deficiency and tuberculosis. For study (2) the subjects will also have the above phrase included in their verbal and written consent discussions. They will be further told that a potential benefit to society of improving TB therapy with the supplementation of cheap, non toxic vitamins is extremely significant, particular in areas of the world where HIV and MDR-TB are highly prevalent, such as possibly their own home countries.

N. Alternative Therapies

There are no alternative therapies used in this trial.

O. Compensation to Subjects

The subjects will be compensated by a $50.00 fee for participating in the study. All transportation to and from DOH clinic will be reimbursed.

P. Costs to Subjects

No costs will be accrued by subjects.

Q. Minor as Research Subjects

No minors will be used as research subjects.

R. Radiation or Radioactive Substances

The patients will receive CXR to follow pulmonary lesion size during the study. There is minimal dose of radiation during a standard CXR and the patients will not be exposed to any more radiation than they normally would have been during routine clinical monitoring.

To notice the association between malnutrition and tuberculosis is not by any means to make a novel observation. Tuberculosis has been called "phthisis" or "to waste away" by the Greeks or "consumption" in the 18th and 19th century.[21]

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