Poor Micronutrient Status of Active Pulmonary Tuberculosis Patients in Indonesia

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ABSTRACT Malnutrition is observed frequently in patients with pulmonary tuberculosis (TB), but their nutritional status, especially of micronutrients, is still poorly documented. The objective of this study was to investigate the nutritional status of patients with active TB compared with that of healthy controls in Jakarta, Indonesia. In a case-control study, 41 out-patients aged 15–55 y with untreated active pulmonary TB were compared with 41 healthy controls selected from neighbors of the patients and matched for age and sex. Cases had clinical and radiographic abnormalities consistent with pulmonary TB and at least two sputum specimens showing acid-fast bacilli. Anthropometric and micronutrient status data were collected. Compared with the controls, TB patients had significantly lower body mass index, skinfold thicknesses (triceps, biceps, subscapular, suprailiac), mid-upper arm circumference, proportion of fat, and concentrations of serum albumin, blood hemoglobin, plasma retinol and plasma zinc, whereas plasma zinc protoporphyrin concentration, as a measure of free erythrocyte protoporphyrin concentration, was greater. When patients and controls were subdivided on the basis of nutritional status, concentrations of serum albumin, blood hemoglobin, and zinc and retinol in plasma were lower in malnourished TB patients than in well-nourished healthy controls, well-nourished TB patients and malnourished healthy controls. In conclusion, the nutritional status of patients with active pulmonary TB was poor compared with healthy subjects, i.e., significantly more patients were anemic and more had low plasma concentrations of retinol and zinc. Low concentrations of hemoglobin, and of retinol and zinc in plasma were more pronounced in malnourished TB patients.

KEY WORDS: • malnutrition • tuberculosis • vitamin A • zinc • micronutrient • humans

Tuberculosis (TB)** is on the increase throughout the world and is one of the most important causes of death among adults in developing countries. In 1993, the WHO declared TB to be a “global health emergency” (Reichman 1996). In Indonesia, TB is one of the most important public health problems with a prevalence of 0.29%, and 5.6% of the world's 7.5 million new cases of TB in 1990. TB ranks second among the leading causes of death in Indonesia (Household Health Survey 1995). Pulmonary TB, a chronic infectious disease caused by Mycobacterium tuberculosis, is characterized by prolonged cough, hemoptysis, chest pain and dyspnea. Systemic manifestations of the disease include fever, malaise, anorexia, weight loss, weakness and night sweats (Hopewell 1994).

Although malnutrition has been described in TB patients previously (Onwubalili 1988, Saha and Rao 1989, Tsukaguchi et al. 1991), contrary to what is commonly believed, little is known about nutritional status with respect to the micronutrients vitamin A, zinc and iron. Low concentrations of these nutrients may affect host defense. Vitamin A deficiency was found to be common among adults with TB and human immunodeficiency virus (HIV) infection in Rwanda (Rwan- ganbwoba et al. 1998). In the prechemotherapeutic era, cod liver oil rich in vitamins A and D was used regularly for the treatment of TB in an attempt to strengthen host defenses (Goldberg 1946). More recently, in vitro studies have shown that retinoic acid can inhibit multiplication of mycobacterium in macrophages (Crowle and Ross 1989). In addition, vitamin A has a vital role in lymphocyte proliferation and in maintaining the function of epithelial tissues (Chandra 1991). Zinc...
SUBJECTS AND METHODS

Subjects. Cases were out-patients with untreated active pulmonary TB admitted to the Rumah Sakit Umum Nasional Cipto Mangunkusumo, which is a major general public hospital and the national referral hospital in Central Jakarta, Indonesia. Controls were healthy subjects with no history of pulmonary TB, matched with cases for sex and age, and selected randomly from nonfamily neighbors of the patients in the smallest administrative unit in Indonesia (rakun tetangga), usually comprising ~20 houses and 100 persons. Field workers asked the head of the administrative unit (rakun tetangga) for a list of healthy subjects of the same sex and age (within ±2 y) as the patients. One person was selected at random as a control from the list of 3–7 persons proposed. Selection of cases was based on the following criteria: 15–55 y at least. Two controls per case and of all test results showed 46% were regarded as being malnourished if BMI < 18.5 kg/m² (James et al. 1988). Biceps, triceps, subscapular and suprailiac skinfolds on the left side of the body were measured to the nearest 0.2 mm three times at each site using a Holtain skinfold caliper (Holthain, Crosswell, Cymrych, Dyfed, UK) (Gibson 1990). Calculations of proportion of total body fat and fat-free mass were based on anthropometric data using the equations of Durnin and Womersley (1974). Mid-upper arm circumference was measured with a flexible steel tape (Gibson 1990).

Two field workers were trained and standardized by one of the authors (E.K.) to take all of the anthropometric measurements. At the end of the standardization period, the technical error of the measurements was determined. The mean technical error, expressed as a standard deviation (s = d/n, where d is the difference between paired measurements and n is the the number of subjects) was 0.13 cm for mid-upper arm circumference, 0.35 mm for biceps skinfold, 0.22 mm for triceps skinfold, 0.31 mm for subscapular skinfold and 0.26 mm for suprailiac skinfold.

Blood samples (15 mL) were collected from fasting subjects via venipuncture to determine total white blood cell count, hematocrit, erythrocyte sedimentation rate (ESR), albumin and hemoglobin in blood and zinc protoporphyrin (ZPP) in erythrocytes. Plasma was prepared by centrifugation at 750 × g for 10 min at room temperature. All biochemical tests above were carried out on the same day. Plasma was stored at −20°C until analysis of C-reactive protein (CRP), retinol, α-tocopherol and zinc. Hemoglobin concentration, hematocrit, white blood cells, ASAT and ALAT were measured directly using an automatic analyzer (Sysmex Microdilutor F-800, Kobe, Japan). The intra- and interassay CV for hemoglobin were <5%, ESR was measured by the Westergren technique (Kohli et al. 1975). Albumin was determined by the bromocresol green method (Dumas et al. 1997). Hemoglobin, hematocrit, white blood cells, ESR and albumin were all measured in Multilab Laboratory, Jakarta, which collaborates with the pulmonary clinic. ZPP as a measure of free erythrocyte protoporphyrin was measured in duplicate using the portable front-face hematofluorometer (AVIV Biomedical, Lakewood, NJ) at the SEAMEO-TROPMED laboratory at the University of Indonesia (Hastika et al. 1992). Variability based on duplicate ZPP measurements was 1.6%. CRP was measured at the University Medical Centre, Nijmegen, using an immunoturbidimetric (Behringewerke, West Germany) method (Metmary et al. 1983). Variability based on analysis of 15 samples was 2.6%. Plasma retinol and α-tocopherol were measured using HPLC with a C-18 column (Bondapak, Waters, Milford, MA); a UV detector (model SPD-6AV, Shimadzu, Tokyo); and methanol/water (95:5, v/v) as mobile phase at the Nutrition Research and Development Center of the Department of Health in Bogor, Indonesia (Arroyave et al. 1982) using standards from Sigma (St. Louis, MO). Plasma zinc was measured using atomic absorption spectrometry (Prasad et al. 1965) in the laboratory of Clinical Chemistry and Hematology, University of Bonn, Germany with values of a quality control analyzed with each set of determinations within 3% of certified values.

Food intake was assessed on the basis of two consecutive 24-h recalls (Bingham et al. 1988) to estimate the intake of energy, protein, fat, carbohydrate, vitamin A, zinc, iron and vitamin E. The two recalls were conducted on two consecutive weekdays. The 24-h diet recall was collected by two interviewers trained by one of the authors (E.K.). Each 24-h recall was conducted using a standardized four-stage protocol (Gibson 1993). First, a complete list of all food and beverages consumed during the previous day was obtained. Second, detailed descriptions of all of the food and beverages consumed, including the cooking methods and brand names were recorded, together with the time and place of consumption. Third, estimates of the amounts of all foods and beverages consumed were recorded by referring to two- and three-dimensional models, household measuring and serving utensils (e.g., spoons, plates or cups), and food packages. Finally, the food recall was reviewed to ensure that all items had been recorded correctly. Part of the training session consisted of determining the differences between the amount estimated by each trainee and the actual weight of the food. An acceptable training level was achieved when the differences between the amount estimated by each trainee and the actual weight of the food was less than 10%.
considered to have been achieved when the average difference between the trainee's estimate and the actual food weight was ≤ 5 g. A pilot study was conducted by observing five patients and five healthy subjects while they ate a meal; the next day, a trained dietary interviewer had these subjects recall what and how much they had eaten at that meal. In general, the subjects accurately described what they had eaten. The calculation of nutrient intake from dietary recalls was done using World Food (Version 2.0, University of California, Berkeley CA), in which the Indonesian food composition tables had been incorporated.

Ethical considerations. The ethical guidelines of the Council for International Organizations of Medical Sciences (1991) were followed and the study was approved by the Committee on Health Research Ethics, Faculty of Medicine, University of Indonesia, Jakarta. Informed consent was obtained from each subject before the start of the study.

Statistical analysis. A one-sample Kolmogorov-Smirnov test was used to check whether data were normally distributed. Mean and standard deviation (SD) are used for reporting normally distributed data. The SPSS software package (Windows version 7.5.2, SPSS, Chicago, IL) was used to assess the differences between patients and controls for normally distributed parameters, whereas differences in nonnormally distributed parameters were tested using the Mann-Whitney test. A multiple stepwise regression analysis was performed to predict concentrations of plasma retinol and zinc by using age, sex, BMI, body temperature, presence of pulmonary cavity, white blood cell count, ESR and concentrations of CRP, and albumin as independent variables. Differences in prevalence were tested with a χ² test. The SPSS software package (Windows version 7.5.2, SPSS, Chicago, IL) was used for all statistical analyses and a P-value < 0.05 was considered significant.

RESULTS

Four patients were withdrawn because they had severe hemoptysis during data collection and required intensive treatment. Thus, 41 (25 men and 16 women) active pulmonary TB patients (cases) and 41 healthy control subjects (25 men and 16 women) aged 28 ± 9 years (mean ± SD) were included in the study. Thirty-four patients (83%) compared with 36 controls (88%) had a BCG-scar on clinical examination. Symptoms and signs of patients were presented as follows: fever (>38°C) (88%), cough >1 month (93%), night sweats (61%), hemoptysis (51%), dyspnea (68%), chest pain (63%) and loss of appetite (76%). Of the cases, 26 (63%) had three positive smears and a remaining 15 (37%) had two positive smears for acid-fast bacilli, whereas 24 (59%) of cases had a positive sputum culture. The radiographic signs of patients were as follows: all patients had lung infiltration, 14 had pulmonary cavities, one had miliary disease and one had pleural effusion. Because the prevalence of HIV infection in this area was low (from the available data, possibly <2%), no testing for HIV was carried out.

The mean BMI in all patients was 20% lower than in controls (P < 0.001), and the mean proportion of fat in all patients (17.7%) was lower than in controls (21.9%) (P < 0.05). The number of patients with BMI < 18.5 kg/m² (66%) was more than sixfold that of the healthy controls (10%) (P < 0.001). The mean body weight, BMI, skinfold thickness, mid-upper arm circumference, proportion of fat, fat mass and fat free mass in male patients were significantly lower than in male controls, whereas all of these variables except biceps and supraclavicular skinfold thickness were significantly different between female patients and controls (Table 1). Serum albumin concentration was 10% lower in TB patients than in controls (Fig. 1). Serum albumin concentration was lower in malnourished TB patients than in well-nourished healthy controls, malnourished healthy controls and well-nourished TB patients (P < 0.05 for all comparisons) (Table 2).

Compared with controls, TB patients had 13% lower mean concentrations of hemoglobin (Fig. 1) and 11% lower mean hematocrit (P < 0.001). In malnourished TB patients, the mean concentrations of hemoglobin were 16% lower than in well-nourished controls, and 11% lower than in malnourished controls (Table 2). The median CRP concentration in TB patients was significantly higher than in controls (Fig. 1). Of the TB patients, 24 had hemoglobin concentrations indicating anaemia, whereas only 9 controls had hemoglobin concentrations below normal (Fig. 2). The median concentrations of erythrocyte ZPP in TB patients were significantly higher than in controls (P < 0.001) with 32 patients and 14 controls having concentrations above normal (>40 µmol/mol heme). The mean white blood cell count (8626 ± 3207 vs. 6434 ± 1712 cells/mm³) and the median ESR were significantly lower in patients (52, interquartile range: 25–82 mm/h) than in controls (22, interquartile range: 12–31 mm/h) (P < 0.01 for both variables).

The mean plasma retinol concentration in patients was significantly lower than in controls with 10 (33%) patients and 4 controls (13%) having plasma retinol concentrations < 0.70 µmol/L, indicating marginal vitamin A deficiency (Fig. 3).

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
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<tr>
<td>n</td>
<td>25</td>
<td>16</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>50.6 ± 9.6</td>
<td>40.8 ± 6.5</td>
<td>58.1 ± 7.3**</td>
<td>50.5 ± 9.9**</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.1 ± 6.3</td>
<td>151.5 ± 5.3</td>
<td>163.0 ± 5.1</td>
<td>151.5 ± 4.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>18.5 ± 3.2</td>
<td>17.8 ± 3.1</td>
<td>21.9 ± 2.8**</td>
<td>21.9 ± 3.5**</td>
</tr>
<tr>
<td>Biceps skinfold, mm</td>
<td>5.5 ± 2.8</td>
<td>6.3 ± 3.8</td>
<td>7.3 ± 2.6*</td>
<td>8.9 ± 4.4</td>
</tr>
<tr>
<td>Triceps skinfold, mm</td>
<td>7.0 ± 3.7</td>
<td>12.1 ± 5.4</td>
<td>9.2 ± 3.2*</td>
<td>17.1 ± 5.5*</td>
</tr>
<tr>
<td>Subscapular skinfold, mm</td>
<td>8.5 ± 3.8</td>
<td>11.0 ± 5.1</td>
<td>11.5 ± 3.9*</td>
<td>14.2 ± 3.9*</td>
</tr>
<tr>
<td>Supraclavicular skinfold, mm</td>
<td>9.2 ± 5.2</td>
<td>11.6 ± 5.4</td>
<td>13.4 ± 5.5*</td>
<td>14.0 ± 5.0</td>
</tr>
<tr>
<td>Mid-upper arm circumference, cm</td>
<td>24.0 ± 3.4</td>
<td>22.3 ± 3.2</td>
<td>28.4 ± 2.5***</td>
<td>26.6 ± 3.5***</td>
</tr>
<tr>
<td>Proportion of fat, g/100 g body</td>
<td>13.5 ± 6.3</td>
<td>23.0 ± 6.2</td>
<td>17.3 ± 5.1*</td>
<td>27.9 ± 4.5*</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>7.3 ± 5.0</td>
<td>9.6 ± 3.8</td>
<td>10.4 ± 3.9*</td>
<td>14.4 ± 5.0**</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>43.4 ± 5.6</td>
<td>31.2 ± 3.8</td>
<td>47.8 ± 4.4**</td>
<td>36.0 ± 5.2**</td>
</tr>
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</table>

1 Values are mean ± SD. Asterisks indicate significantly different from same sex patients, * P < 0.05; ** P < 0.01; *** P < 0.001 (independent sample t test).
2). If TB patients with plasma CRP concentrations ≥ 10 mg/L are excluded, the proportion with marginal vitamin A deficiency was 25%. No controls had elevated plasma CRP levels. In malnourished TB patients, the mean plasma retinol concentration was 32% lower than in well-nourished healthy controls \( (P < 0.05) \), 27% lower than in well-nourished TB patients and 18% lower than in malnourished healthy controls \( (P < 0.01) \) (Table 2). Similarly plasma zinc concentrations in patients were significantly lower than those in controls with eight patients and two controls having plasma zinc concentrations < 10.7 mmol/L (Fig. 2). The mean plasma zinc concentration in malnourished TB patients was 13% lower than in well-nourished healthy controls \( (P < 0.05) \) and was 7% lower than in well-nourished TB patients. Compared with malnourished healthy controls, malnourished TB patients had 10% lower mean plasma zinc concentration (Table 2). The mean plasma α-tocopherol concentration in patients was not significantly different from that in controls. However, 16 patients and 10 controls had serum α-tocopherol concentrations below normal (< 11.5 mmol/L) (Fig. 1).

In a stepwise multiple regression analysis, plasma retinol concentration in patients was significantly associated with BMI \( (b = 0.672, P = 0.008) \) and age \( (b = 0.476, P = 0.032) \). BMI, 18.5 kg/m²

<table>
<thead>
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<th>TABLE 2</th>
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<tr>
<td>Comparison of biochemical variables in tuberculosis (TB) patients and healthy controls on the basis of their nutritional status</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>BMI &gt; 18.5 kg/m²</th>
<th>Albumin (g/L)</th>
<th>Hemoglobin (g/L)</th>
<th>Retinol (μmol/L)</th>
<th>Zinc (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>47.7 ± 6.0a (30)</td>
<td>136.6 ± 13.5a (37)</td>
<td>1.32 ± 0.6a (26)</td>
<td>13.8 ± 0.4a (25)</td>
</tr>
<tr>
<td>TB patients</td>
<td>47.0 ± 7.0a (11)</td>
<td>129.4 ± 19.3a (14)</td>
<td>1.22 ± 0.5ab (9)</td>
<td>12.9 ± 0.7ab (13)</td>
</tr>
<tr>
<td>BMI &lt; 18.5 kg/m²</td>
<td>Healthy controls</td>
<td>47.6 ± 5.0a (3)</td>
<td>128.5 ± 8.5ab (4)</td>
<td>1.09 ± 0.6ab (4)</td>
</tr>
<tr>
<td>TB patients</td>
<td>41.7 ± 6.0b (21)</td>
<td>114.8 ± 19.2b (27)</td>
<td>0.89 ± 0.4b (21)</td>
<td>12.0 ± 2.4b (25)</td>
</tr>
</tbody>
</table>

1 Values are mean ± sd. Values in the same column without a common superscript are different \( P < 0.05 \), using least significant differences multiple comparisons test.
Intakes of energy, carbohydrate, fat, protein, vitamin A and iron tended to be lower ($P = 0.20–0.93$) in patients than in controls (data not shown).

**DISCUSSION**

We demonstrated that the nutritional status assessed by measuring weight, height, mid-upper arm circumference, skinfold thicknesses and serum albumin was significantly lower in patients with active pulmonary TB compared with healthy controls. These data corroborate those found in England (Onwubalili 1988), India (Saha and Rao 1989) and Japan (Tsukaguchi et al. 1991). As in our study, TB patients had significantly lower BMI, skinfold thickness and serum albumin concentration than healthy controls. Malnutrition per se had a more pronounced effect on serum albumin concentration in TB patients. As a result, serum albumin concentration in malnourished patients was lower than that in well-nourished healthy controls, well-nourished patients and malnourished healthy controls. Lower values of transthyretin (previously referred to as prealbumin) and retinol-binding protein were reported in the Indian and Japanese studies. The poorer nutritional status of patients with pulmonary TB may be due to anorexia (Hopewell 1994), impaired absorption of nutrients or increased catabolism. Energy and nutrient intake tended to be lower in TB patients than in controls, but the differences were not significant. Two 24-h recalls are not sufficient to determine whether patients have a lower energy intake than controls (Bingham et al. 1988). Because the number of subjects or number of days required to obtain significant differences are much higher, it may be preferable to use another method to determine food intake. On the other hand, patients and controls may have similar food habits and food intakes because their socioeconomic background and living conditions are similar. Thus, infectious disease such as TB may lead to impaired absorption and increased rates of metabolism (Ginzburg and Dadamukhamedov 1990, Ulijaszek 1997). The disease-induced production of cytokines such as interleukin-6 and tumor necrosis factor-$\alpha$ may induce fever, hepatic synthesis of acute phase reactant proteins, inhibit production of serum albumin and cause dramatic shifts in plasma concentration of certain essential micronutrients (Beisel 1998). TB is probably associated with more severe malnutrition than other chronic illnesses; in the Indian study referred to above (Saha and Rao 1989), the nutritional status of the patients with TB was worse than that of those with leprosy.

Concentrations of selected micronutrients tested in our TB patients were significantly lower than in controls. Low concentrations of hemoglobin and of retinol and zinc in plasma in malnourished patients were more pronounced than in healthy controls and well-nourished patients. Furthermore, the prevalence of low concentrations of vitamin A and zinc and of anemia was higher in patients than in controls. Low concentrations of retinol in plasma can be due to a number of factors, including reduced intake or reduced absorption of fat. In addition, the infection itself can compromise vitamin A status in a number of ways. It can increase urinary excretion of vitamin A as has been shown in patients with fever, e.g., due to pneumonia and shigellosis (Mitra et al. 1998b, Stephensen et al. 1994). During the acute phase response, leakage of transthyretin (prealbumin) and albumin through the vascular endothelium occurs, and production of retinol-binding protein and transthyretin by the liver is reduced (Fleck and Myers 1985). Finally, low serum retinol levels can also result from increased utilization of retinol by tissues (Fleck and Myers 1985). It is likely that a combination of mechanisms is operative in TB patients.

In our study, however, low plasma retinol concentration did not correlate significantly with acute phase markers (CRP concentration and ESR). By contrast, a study in children with shigellosis showed that the serum concentration of CRP was negatively correlated with that of serum retinol (Mitra et al. 1998a). CRP is an acute phase protein whose concentration changes rapidly as a result of infection. Thus, CRP was probably not the best choice of protein to control for the acute phase changes in plasma micronutrients during a chronic illness such as TB. Therefore, it is not really surprising that CRP did not correlate with micronutrient measures. In addition, this finding may suggest that low plasma retinol is a result of a primary deficiency.

Plasma zinc concentrations were significantly lower in TB patients than in controls, in agreement with a study in India (Taneja 1990). This was likely due to redistribution of zinc from plasma to other tissues (Filteau and Tomkins 1994) or reduction of the hepatic production of the zinc-carrier protein $\alpha_2$-macroglobulin and to a rise in the production of metallothionein, a protein that transports zinc to the liver (Gabay and Kushner 1999). This agrees with our finding that ESR was negatively correlated with plasma zinc concentration although not with CRP.

In TB patients in this study, concentrations of hemoglobin were significantly lower and those of ZPP were significantly higher than in controls. Elevated concentrations of ZPP, a measure of free erythrocyte protoporphyrin, are indicative of iron-deficient erythropoiesis (Hastka et al. 1992). These results are not affected by the acute phase response as shown here, i.e., ZPP did not significantly correlate with CRP levels. Low iron status, as measured by low serum iron concentration and total iron-binding capacity, has also been reported in pulmonary TB patients in England (Onwubalili 1988). There are two explanations for the association of low iron status with infection. One is that anemia results from chronic infection. The other, which is more speculative, is that iron deficiency would increase susceptibility to an infection such as TB. In this context, it is relevant that cell-mediated immunity becomes compromised in iron deficiency (Dallman 1987) before anemia becomes apparent.

In conclusion, this study shows that the nutritional status of patients with active pulmonary TB was poor compared with healthy controls. The prevalence of anemia and low concentrations of plasma retinol and zinc was significantly higher in patients than in controls. The low concentrations of hemoglobin, and of retinol and zinc in plasma were more pronounced in malnourished TB patients. Further studies are required to establish the role of these low concentrations in host defense against TB.

**LITERATURE CITED**


