Original Article

Energy regulation in newly diagnosed TB with chronic energy deficiency: free fatty acids and RBP4

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Background and objectives: Energy metabolism may be dysfunctionally integral between host and infective agent in active tuberculosis, mediated by adipocytokines and free fatty acids (FFA) as the products of triglyceride lipolysis in fat, blood or other tissues. Retinol Binding Protein 4 (RBP4) and asymmetric dimethylarginine (ADMA) are candidate adipocytokines. The possibility of a deleterious metabolic nexus in chronic energy deficiency (CED) (BMI <18.5 kg/m^2) is explored. **Methods and design:** Newly diagnosed patients with tuberculosis (n=63) were selected using consecutive random sampling at a Centre for the Care and Treatment of Lung Diseases in Makassar, Indonesia. Diagnosis of pulmonary TB required microscopy with Ziehl-Neelsen stain. Anthropometric measurements were taken. Venesection allowed glomerular filtration rate, FFA, serum glutamic oxaloacetic transaminase and glutamate-pyruvate transaminase to be assessed. **Results:** CED was evident in 60.3%. For the well and lesser nourished, medians were, respectively, FFA 0.30 and 0.37 mmol/mL (p=0.960); RBP4 199730 ng/mL and 11721 ng/mL (p=0.009); GFR 106 ml/min and 113 ml/min (p=0.673); and ADMA 0.52 ng/mL and 0.51 ng/mL (p=0.172). BMI and serum RBP4 were correlated (ρ=0.52, p<0.001), with odds ratios (OR) 5.8 (CI 1.68-20.3). RBP4 in CED was lower than in better nourished patients. Serum FFA is not evidently associated with BMI in patients with active TB. **Conclusions** : RBP4 is some 6-fold lower when active TB patients have CED than when BMI >25 kg/m^2. However, FFA was not associated with CED in these active TB patients which may be a type 2 error or represent an energy impasse where infection and the host's metabolic needs are in competition.

Key Words: tuberculosis, malnutrition, free fatty acids, retinol binding protein 4, asymmetric dimethylarginine

INTRODUCTION

Tuberculosis (TB) is an infectious disease associated with considerable morbidity and mortality worldwide. Among patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), it is the second most common cause of death.[1] Indonesia has the fourth-highest rate of TB in the world, after India, China, and South Africa, and approximately 0.4–0.5 million new cases are diagnosed each year. Some 75% of patients with TB in Indonesia are in the reproductive age group (15–45 years).[2]

TB is associated with fat metabolic disorders. The adipocyte cell produces free fatty acids (FFAs) and inflammatory mediators (adipokines), such as RBP4 and asymmetric dimethylarginine (ADMA). Plasma ADMA is inversely related to the mass of visceral fat, which acts to stimulate the oxidation of fatty acids (lipolysis) by inhibiting nitric oxide synthesis (NOS), and causing a decreased production of nitric oxide (NO). *Mycobacterium tuberculosis* infection causes an inflammatory response involving the release of inflammatory cytokines, which can cause malnutrition through the stimulation of lipolysis and proteolysis and an increase in leptin.[3]

Serum FFAs are a product of the breakdown of serum triglycerides in chylomicrons or VLDL and are mobilized from fat tissue, especially into the splanchnic circulation from omental fat for presentation to the liver. They serve as an energy substrate and intracellular storage for muscle and fat cells and stimulate hepatic gluconeogenesis.[4] FFAs in plasma are bonded to albumin unless binding

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sites are exceeded. Serum FFAs are utilised and synthesised by *M. tuberculosis*.[5] One study found that serum FFAs are higher in patients with untreated pulmonary TB than in healthy individuals and patients with pulmonary TB who have been receiving treatment.[6]

Some studies have shown that patients with TB commonly have retinol (vitamin A) deficiency. Vitamin A plays an important role in the immune system of patients with TB; retinoic acid, transported bound to albumin,[7] stimulates the differentiation of monocytes, thus inhibiting the multiplication of *M. tuberculosis* in macrophages, which induces vitamin A deficiency and imbalances the regulation of T helper cells.[8] Serum retinol binding protein 4 (RBP4) is lowered by retinoic acid[9] and is a specific transporter protein that plays a role in cell proliferation, differentiation, and apoptosis. In one study, lower RBP4 was found to improve acute phase protein status and alleviate malnutrition.[10] Some studies have found low vitamin A after anti-TB drug therapy, even with vitamin A supplementation.[11] Moreover, RBP4 contributes to insulin resistance and the risk of diabetes.[12] RBP4 may be a biomarker for TB although this may be related to its activity as an inflammatory cytokine and to its retinol transport function.[13] There is a need to evaluate ADMA, FFA, and RBP4 in patients with pulmonary TB in Indonesia. The hypothesis that a deleterious synergy in energy metabolism, reflected in fatty acid flux and oxidation with insulin resistance, is central to the expression of active TB is shown in Figure 1.

MATERIALS AND METHODS

Location, research design, and study population

This analytic, observational, cross-sectional study was conducted at the Center for the Care and Treatment of Lung Diseases, Makassar (BP4). Outpatients were enrolled using consecutive random sampling. They fulfilled the following criteria: age 18–60 years; no diagnosis of HIV/AIDS; a recent diagnosis of pulmonary TB with identification of acid-resistant bacteria in a microscopic examination of at least two of three sputum preparations evaluated with the Ziehl Neelsen stain (the standard screening method of WHO), or according to culture results; a glomerular filtration rate (GFR) >60 mL/min/1.72 m^2 (calculated using the Modification of Diet in Renal Disease [MDRD] equation); serum glutamic oxaloacetic transaminase (SGOT) and serum glutamate-pyruvate transaminase (SGPT) less than three times the normal value (SGOT <114, SGPT <123); and provision of written informed consent for participation. The research plan was approved by the Ethics Commission of the Faculty of Medicine of Universitas Hasanuddin.

Data collection

Biomedical data (name, sex, age and medical history) were obtained from interviews conducted by trained personnel using a questionnaire. Body measurements for height and body weight using a stadiometer (200-cm capacity and a level of accuracy of 0.1 cm) and a TANITA scale (150-kg capacity and a level of accuracy of 100 g). Patients were barefoot and wearing minimal clothes. Measurements were performed three times to obtain accurate results, and BMI was calculated as weight divided by height squared (kg/m^2). Chronic energy deficiency (CED) was defined as a BMI <18.5 kg/m^2.[14] Blood sampling and laboratory testing were performed at the BP4.

Data analysis

The data were analyzed by SPSS version 17. The limit of significance was an alpha value of 5% or $p<0.05$. To assess differences in characteristics between TB patients by nutritional status, Mann-Whitney U test and Student's t test were performed. Spearman's rank correlation test was used to evaluate correlation between variables and levels of RBP4, ADMA, FFA serum. To evaluate the impact of low levels of RBP4 on the risk of malnutrition (underweight), chi-square test was performed with confidence interval of 95%. All data was converted into categorical variables, cut off point levels of RBP4 used was 12700 ng/mL, because the RBP4 levels in normal sample were 12700-48600 ng/mL, ADMA cut off point used was 0.3 and FFA was 0.297 mmol/mL.

RESULTS

Patient characteristics are shown in Table 1. Among the

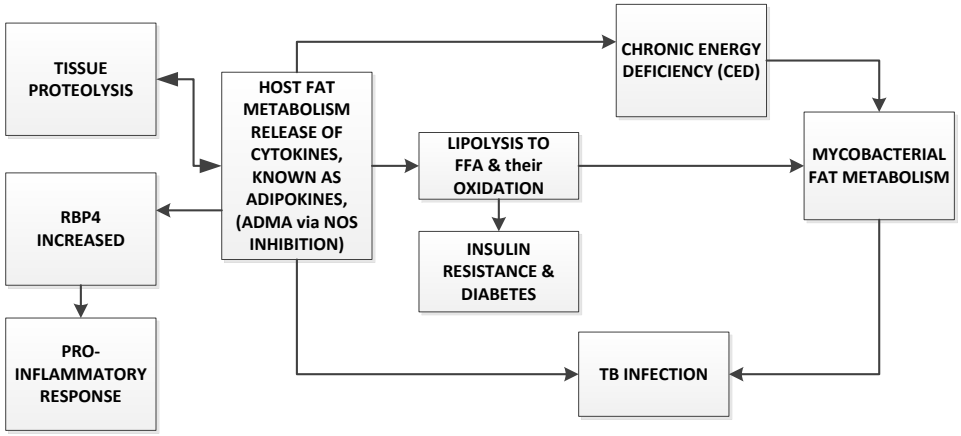

Figure 1. Pathogenetic model for the host-mycobacterial interrelationships in energy metabolism. FFA: free fatty acid; RBP4: retinol binding protein; ADMA: asymmetric dimethyl arginine; NOS: nitric oxide synthase.

Table 1. Demographic characteristic of malnourished and well-nourished and groups

Characteristic	Malnourished (n=38)		Well-nourished (n=25)	
	n	%	n	%
Sex				
Men	22	57.9	20	80
Women	16	42.1	5	20
Occupation				
Farmer	1	2.6	3	12
Fisherman	-	-	2	8
Self-employed	7	18.4	7	28
Labor	10	26.3	5	20
Pedicab	-	-	1	4
Housewife	6	15.8	5	20
Unemployment	11	28.9	2	8
Other	3	7.9	-	-
Smoking duration (yrs)				
0	20	52.6	8	32
1-5	2	5.3	1	4
5-10	5	13.2	3	12
>10	11	28.9	13	52
Age (yrs)				
18-28	13	34.2	1	4
29-39	14	36.8	9	36
40-50	5	13.2	9	36
51-60	6	15.8	6	24

Malnourished indicates that CED was evident with a BMI <18.5 kg/m^2, Well-nourished indicates that CED was evident with a BMI ≥18.5 kg/m^2.

Table 2. Differences in selected variables by nutritional status

Variable	Nutritional status		*p*
	Malnourished (n=38) Median (range)	Well-nourished (n=25) Median (range)	
Age (yrs)	32.5 (20.0-59.0)	42.0 (20.0-57.0)	0.012
BMI (kg/m^2)†	16.0 (±1.78)	20.3 (±1.78)	0.001
Hb (g/dL)†	12.3 (±1.67)	12.5 (±1.53)	0.769
Leucocyte (10^3/µL)†	9.8 (±3.6)	11.3 (± 3.6)	0.111
SGOT (U/L)	31 (13.0-97.0)	30 (19.0-64.0)	0.509
SGPT (U/L)	22 (10.0-103)	22 (11.0-77.0)	0.860
GFR (ml/min)	106 (64.6-1429)	113 (73.3-1339)	0.673
RBP4 (ng/mL)	11721 (340-48961)	19973 (4586-43854)	0.009
ADMA (ng/mL)	0.51 (0.05-1.07)	0.52 (0.32-0.85)	0.715
FFA (mmol/mL)	0.37 (0.04-1.41)	0.30 (0.06-0.94)	0.960

SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; GFR: glomerulus filtration rate; RBP4: retinol binding protein 4; ADMA: asymmetric dimethylarginine; FFA: free fatty acid.
Malnourished indicates that CED was evident with a BMI <18.5 kg/m^2, well-nourished indicates that CED was evident with a BMI ≥18.5 kg/m^2.
†Mean (SD).

participants, 25 were well nourished (39.7%) and 38 were malnourished (60.3%). There were 42 men (66.7%) and 21 women (33.3%). The well-nourished group consisted of 20 men (80%) and 5 women (20%), whereas the malnourished group consisted of 22 men (57.9%) and 16 women (42.1%). In the malnourished group, 28.9% of the patients were unemployed, and in the well-nourished group 28.0% of the patients were self-employed. In the well-nourished group, 52% of the patients had a smoking history of more than 10 years, whereas 52.6% of the malnourished group had never smoked (52.6%). Among both groups, most of the patients were aged 29–39 years.

To assess differences in characteristics between well-nourished and malnourished patients with TB, Mann–Whitney and independent *t* tests were performed. Table 2 shows that there were no significant differences between patients with acceptable BMIs and those with CED: Hb 12.5 g/dL, and 12.3 g/dL; p=0.769, leucocyte counts 11.3 µL and 9.8 µL (p=0.111), the median SGOT were 30 u/l and 31 U/L (p=0.509), GFR was 106 ml/min and 113 ml/min (p=0.673), ADMA were 0.52 ng/mL and 0.51 ng/mL (p=0.1715), and FFA were 0.30 and 0.37 mmol/mL (p=0.960). Significant differences were found in BMI: 16.0 kg/m^2 in the malnourished group and 20.3 kg/m^2 in the well-nourished group (p<0.001). The median level of RBP4 was 11721 ng/mL in the malnourished patients and 19973 ng/mL in the well-nourished group (p=0.009).

Correlations between serum RBP4, ADMA, and FFA and BMI in patients with pulmonary TB

To evaluate the correlation and strength of correlation

Table 3. Spearman's rank correlation coefficient and OR (95% CI) on BMI with serum RBP4, ADMA and FFA in patients with TB

Variable	BMI		Underweight†		
	Rho (ρ)	*p*	OR	CI 95%	*p*
RBP4	0.52	0.001	5.83	1.68-20.3	0.004
ADMA	0.44	0.731	0.921	0.84-1.01	0.270
FFA	-0.22	0.866	1.032	0.30-0.35	1.00

RBP4: retinol binding protein; ADMA: asymmetric dimethylarginine; FFA: free fatty acid.
The strength of the correlation can be seen from the correlation coefficient (ρ).
Non parametric correlation of Spearman test. Chi square test to estimate the association defined as OR.
†Cut-off point of underweight is BMI <18.5 kg/m^2.

between multiple variables and levels of RBP4, ADMA, and serum FFA, Spearman's correlation test was performed because the data were not normally distributed. Table 3 shows a strong positive correlation for the entire population between BMI and RBP4 (p<0.001), with moderate correlation strength (ρ=0.52), but no significant correlation was found between BMI and the serum FFA (p=0.866) or between nutritional status and the ADMA (p=0.731).

Estimated correlation between nutritional status and low RBP4, high ADMA, and high FFA

To evaluate the correlation of malnourished with low levels of RBP4, the chi-square test was performed with a 95% confidence interval. All data were converted into categorical variables, and the cut-off point of RBP4 was 12700 ng/mL because the RBP4 levels in the normal sample were 12700–48600 ng/mL. The ADMA cut-off point was 0.3 and that of FFA was 0.297 mmol/mL. Table 3 shows a significant relationship between nutritional status and the RBP4 level (p=0.004, OR=5.83).

DISCUSSION

The percentages of well-nourished and malnourished patients were consistent with a study conducted in patients newly diagnosed with pulmonary TB in Ghana, which found that 51% were malnourished and 49% were well nourished.[15] The results of the present study were also in accordance with another study which found that 60% of sampled patients with TB had low BMI and that patients with TB were 11 times more likely than others to have BMI <18.5 kg/m^2. This is because TB infection increases the energy required to maintain normal functioning, and cytokine inflammation results in decreased food intake and malabsorption of nutrients as well as changes in body metabolism, thus leading to protein–energy malnutrition.[3] A study conducted in India and Korea showed that BMI, as one of five specific, interacting, developmental factors, are working for and against contemporary TB control programmed in Asian countries and is a widespread problem in developing countries.[16]

BMI and serum RBP4 were positively correlated in patients with pulmonary TB (ρ=0.52, p<0.001).

RBP4 levels were lower in the malnourished patients with pulmonary TB compared with their well-nourished counterparts. This is similar to the findings of a study conducted by Tanaka (2011); in patients with active pulmonary TB in Vietnam and Japan, the median of RBP4 was 17.5 µg/mL, compared with 30.5 µg/L in controls. The lower RBP4 levels in TB patients were caused by acute inflammation, which decreases negative acute phase proteins.[8]

The lower RBP4 in the malnourished group resembled the results of a study in which lower RBP4 was observed in children with protein–energy malnutrition, and increased gradually with energy intake and protein therapy.[17] The low RBP4 in CED are due to low values of the complex factors that determine protein concentration, namely: synthetic rate, secretion rate, intravascular–extravascular transfer, and catabolic speed. The half-life of RBP4 is 12 hours and the synthetic rate is 5 mg/kg/day. When the amino acid substrate for protein synthesis is limited, such as in malnutrition, the protein synthetic rate tends to decline.[17,18] This could explain why CED patients with pulmonary TB in this study were 5.83 times more likely to have lower serum RBP4s than their better nourished counterparts. This study is consistent with a study on women living with HIV in Kenya, which independently found that acute phase response and malnutrition were independently associated with low RBP4.[10]

In the present study, there was no significant correlation between ADMA and nutritional status (p=0.731). This is consistent with a previous study conducted in 49 patients with chronic kidney disease in Turkey,[19] which did not find a significant correlation between ADMA and BMI. This contrasts with a study on 38 patients with stage V chronic renal failure in Italy, which showed an inverse relationship between ADMA and FFA, BMI, and body weight after dialysis.[20] Some 93 healthy patients in Spain showed a positive correlation between ADMA and weight, BMI, and waist circumference, confirming that ADMA has a relationship with several markers for body fat.[21] The study also observed interactions between ADMA and several markers of fat in adults, and obtained ADMA concentrations of 29%–120%, which were higher in obese men than in healthy controls;[21] these results are consistent with those of the present study.

ADMA is a known inhibitor of NO synthesis and is often associated with impaired endothelial function. However, ADMA is also allegedly associated with a number of other risk factors such as obesity, hypertension, hypercholesterolaemia, smoking, diabetes mellitus, hyperhomocysteinaemia, and inflammation.[22] The role of ADMA in inflammatory processes has also been linked with higher SDMA. The ADMA/SDMA ratio provides direct information about DDAH activities. A previous

study found that high ADMA must be accompanied by an increase in the ADMA/SDMA ratio in order to be a marker of malnutrition due to inflammatory processes.[23]

If ADMA is expressed in high concentration in active tuberculosis then NO production from alveolar macrophages could be impaired. A higher ADMA and a lower L-arginine to ADDMA ratio in active tuberculosis might be expected although not observed in the present study, perhaps because of limited sample size.[24]

The lack of correlation between nutritional status and ADMA in this study may be attributable to concomitant clinical abnormalities. ADMA is closely connected with other mediators of inflammation in patients with pulmonary TB.

In the present study, serum FFA was not associated with nutritional status in patients with pulmonary TB. Nevertheless, FFA was higher than in healthy people (0.174–0.297 mmol/mL).[25] These results are consistent with findings in 10 healthy controls and 50 patients with pulmonary TB divided into three groups (minimal lesions, average lesions, and wide lesions).[6] The ages of the sample population ranged from 20 to 50 years. Serum FFA levels in patients with TB were higher than those in the control group (0.459±0.089 mEq/L and 0.852±0.028 mEq/L; $p<0.01$).

Inhalation of *M. tuberculosis* triggers a crucial protective response of the body's cell-mediated immunity, which results in inflammation. Increased production of proinflammatory cytokines such as IL-6, TNF-α, IL-1β, and IFN-Ɣ causes metabolic changes in patients with TB; this is referred to as "anabolic block" at the substrate level, which inhibits the formation of protein and fat synthesis and increases proteolysis and lipolysis, with resultant malnourishment in patients with TB.[26] Malnutrition compromises the immune system in TB, disease severity increasing, and therapeutic effectiveness diminished. In addition, lipolysis yields FFA as a source of energy for TB bacteria and increases their virulence.[5]

M.tuberculosis metabolic complexity and chronicity contributes to weight loss through decreased adipose tissue and lean mass. A decline in peripheral FFA utilisation may also contribute to elevated serum FFA due to inhibition of transcyclase reactions involved in fat formation of neutral lipids or phospholipids and blockade of the entry of fatty acids into the mitochondria.[3] Thus, the combination of excessive production and decreased peripheral utilisation can cause higher serum fatty acids, as observed in this study.

The soluble enzyme system in *M. tuberculosis* catalyses the synthesis of fatty acids that promotes an increase in the number of bacteria through nitrogen metabolism. Conditions such as diabetes mellitus, starvation, alcoholism, and corticosteroid therapy may predispose patients to pulmonary TB because serum FFA tends to be higher. Inhibition of nitrate reductase activity by several anti-TB medication reduces utilisation and synthesis of fatty acids by *M. tuberculosis* and thus limits the growth of pathogens. *M. tuberculosis* uses fatty acids as an energy source when its growth is inhibited by anti-TB medication.[3,27]

Fatty acids as FFA or from serum triglycerides, local tissue fat or intracellular stores, and splanchnic flux during nocturnal fasting with stimulation of hepatic gluconeogenesis, play a crucial role in whole body energy regulation. This is dysregulated in malnutrition, overfatness and insulin resistance or deficiency.[4] Impaired energy regulation (IER) is an over-arching concept which appears to characterise the TB infected patient and the TB organism's pathogenicity in active TB. In turn, fat soluble vitamins and their transport may be implicated in the overall pathogenesis. However, the place of vitamin D and its sunlight-mediated status, or exposure to it, while inevitably involved, remain unclear.[28,29] The present study has examined a possible link with vitamin A (retinol) transport which may be of functional significance or, simply, a marker of malnutrition.[11]

The clinical implication of this analysis is that there should be considerable caution in providing vitamin A supplementation to patients with TB, and that any such supplementation should be combined with sufficient energy and protein intake, ideally food-based.

This study had limitations. It was a cross-sectional study for which sampling was conducted only once; thus, only the correlations, and not causal relationships, could be observed between variables. It is also not a case-control study. Several factors which were not examined, such as vitamin A, SDMA, the ADMA/SDMA ratio, and other inflammatory factors might have affected the associations explored. Co-morbidities have not been taken into account.

Conclusions and recommendations

There is a significant positive correlation for the entire population between BMI and serum RBP4. Serum RBP4 in the CED group was lower than that in the better nourished group; and had a 5.83 time lower serum RBP4. No relationship was observed between BMI and either ADMA or FFA. Further observational studies with healthy controls may enable a better understanding of these relationships. Much remains to be done to explore the general hypothesis that joint host-infectious agent impaired fat-energy regulation might underpin the nexus between CED and active TB. How this might be managed nutritionally is demanding and not likely to be amenable to simplistic micronutrient supplementation.

AUTHOR DISCLOSURES

All authors declare that they have no competing interests. This study was funded by Health Professional Education Quality, Ministry of Research and Technology of Higher Education, Republic Indonesia 2014.

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