Serum PCT and its Relation to Body Weight Gain in Pulmonary Tuberculosis

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Abstract The present study was aimed at assessing alterations in serum PCT in terms of its relation to body weight gain in pulmonary tuberculosis (PTB) patients undergoing treatment. Among patients (25–75 years) diagnosed with pulmonary tuberculosis, those that were new smear positive, showed sputum conversion at the end of 2 months and were declared clinically cured at the end of 6 months, were included in the study ($n = 40$). Serum procalcitonin was determined by BRAHMS PCT-Q kit. Patients were divided into two study groups—Group 1 ($n = 21$; serum PCT > 2 ng/ml at diagnosis), Group 2 ($n = 19$; serum PCT > 10 ng/ml at diagnosis). Body weights of all patients were obtained at three different time points, PTB-0 (at diagnosis), PTB-2 (after 2 months of intensive treatment) and PTB-6 (after 6 months of treatment). In both groups, mean body weights at PTB-2 and PTB-6 were significantly higher than those at PTB-0 and at PTB-6 were significantly higher than those at PTB-2. However, percentage body weight gain following 2 months of intensive treatment was higher in group 1 (4.05 % gain, $p < 0.01$) than in group 2 (2.75 % body weight gain, $p < 0.05$). Thus, the percentage gain in group 1 was

tending more towards the desirable minimum gain of 5 % during intensive phase. Increase in serum PCT levels in pulmonary tuberculosis is inversely associated with body weight gain during treatment. Thus, PCT could play a role in regulation of body weight gain in anorectic conditions like tuberculosis.

Keywords Tuberculosis · Procalcitonin · Body weight · Chemotherapy · Malnutrition

Introduction

Current advances in tuberculosis research have drawn the attention of clinicians to body weight gain during treatment to ensure good prognosis, since wasting is recognized not only as a prominent feature of tuberculosis but also as one of the determinants of the disease severity and outcome [1]. Procalcitonin (PCT) is an acute phase reactant protein and consists of 116 amino acids [2]. It has been reported as a sensitive marker of severe bacterial infection [3, 4]. While some studies implicate a poor diagnostic value to PCT in lower respiratory tract infections like pulmonary tuberculosis [5, 6], some others report that PCT could be a good indicator of inflammation in patients with chronic diseases and in persons exposed to long-lasting infections like tuberculosis [7]. In an earlier study we have reported an increase in serum PCT in patients with pulmonary tuberculosis (PTB). Serum PCT had decreased in a few patients and increased in some others at the end of intensive phase of chemotherapy. However, at the end of continuation phase, serum PCT had decreased in all patients [8]. We have also reported body weight gain in the same set of patients during chemotherapy [9]. While body weight gain during the intensive phase of chemotherapy was less than

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5 %, that during the continuation phase was almost 13 % as compared to body weight at diagnosis. It has been predicted that a weight gain of 5 % or less during the first 2 months of therapy is associated with an increased risk of relapse, even after controlling for other risk factors for relapse [10]. Although the role of serum PCT as a marker in bacterial infections is well established, the function of PCT in humans is not fully understood. Previous authors have reported that administration of amino-PCT (N-PCT), the biologically active fragment of PCT to free-feeding, freely moving unstressed rats significantly reduced food intake in a dose-dependent manner and decreased body weight gain; hence it has the potential to be an important physiological regulator of energy homeostasis. Further, abundant expression of PCT-like immunoreactivity was detected in free feeding rats in regions of the brain implicated for feeding behavior; whereas PCT expression was significantly reduced in fasted rats [11]. These authors have however expressed their view that further research is necessary to assess N-PCT induction in some well-characterized anorexia-eliciting paradigms. These views together with our findings on serum PCT and body weight gain in PTB patients undergoing treatment, prompted us to look at the two parameters as dependent variables and assess whether changes in serum PCT have a bearing on the extent of weight gain during treatment of PTB (a well known anorexia eliciting disease). The present study was aimed at assessing alterations in serum PCT in terms of its relation to body weight gain in pulmonary tuberculosis patients undergoing treatment.

Materials and Methods

Subjects

This was a retrospective study. Among the patients (25–75 years) who attended as outpatients to The Institute of Thoracic Medicine (ITM), Chennai, India between January 2012 and September 2012, those with following criteria were included in the study—diagnosed with pulmonary tuberculosis, new smear positive, showed sputum conversion at the end of 2 months and declared clinically cured at the end of 6 months ($n = 40$, 37 males, 3 females). The diagnosis of tuberculosis was performed using Ziehl–Neelsen staining method for Acid-fast Microscopy (AFM) and culture for growth of the organism on Lowenstein–Jensen (LJ) medium. A new patient was defined as a TB patient who has never had treatment for TB or one who has taken anti-TB drugs for less than 1 month. A smear positive patient was defined as a patient with at least two initial sputum smear examinations (direct smear microscopy) positive for acid-fast bacilli (AFB) or a patient

with one sputum examination positive for AFB and radiographic abnormalities consistent with active pulmonary TB as determined by the treating Medical Officer (MO) or a patient with one sputum specimen positive for AFB and culture positive for *M. tuberculosis*. TB patients declared clinically cured included patients who were initially sputum smear-positive patient, who had complied with and completed treatment and had negative sputum smears, on at least two occasions, one of which was at the end of treatment. Only those PTB patients free from other infectious diseases were included in the study. The patients were also tested for radiographic abnormalities. The study protocol was approved by the Institutional ethics committee and was carried out in accordance with the principle of Declaration of Helsinki.

Methods

Treatment was according to the RNTCP-DOTS protocol with the standard recommended dose of the four-drug regimen (Rifampicin, Isoniazid, Pyrazinamide and Streptomycin) in the intensive phase of first 2 months. After confirming sputum conversion, the patients were continued into the next 4 months of continuation phase with the standard recommended dose of the two drug regimen (Rifampicin and Isoniazid).

Serum procalcitonin was determined by PCT-Q kit that employs immunochromatographic test [12]. Body weights of all patients were obtained at three different time points, labelled as PTB-0 (PTB at diagnosis), PTB-2 (PTB after 2 months of intensive phase of treatment) and PTB-6 (PTB after 6 months of treatment). To study the influence of serum PCT at diagnosis on body weight gain during treatment, patients were divided into two study groups—Group 1 ($n = 21$; males 18, females 3; serum PCT > 2 ng/ml at diagnosis), Group 2 ($n = 19$; males 16, females 3; serum PCT > 10 ng/ml at diagnosis).

Statistical Analysis

Body weight gain during the two phases of treatment was analyzed as percentage gain over body weight during diagnosis. Statistical analysis was carried out using repeated measures ANOVA for comparison of body weights between at PTB-0, PTB-2 and PTB-6 in each study group/subgroup. Following ANOVA for correlated samples, the Tukey HSD posttest was applied to check for significance. For all the tests mentioned, p value of less than 0.05 was considered significant, less than 0.01 very significant and less than 0.001 as extremely significant. The percentage body weight gains and p values at the end of the two phases

Table 1 Mean body weight in Group 1 and Group 2 pulmonary tuberculosis patients at diagnosis (PTB-0), at 2 months post treatment (PTB-2) and 6 months post treatment (PTB-6)

Groups	No. of patients	PCT at diagnosis (ng/ml)	Body weight (kgs)			Mean percentage gain in body weight	
			PTB-0	PTB-2	PTB-6	After 2 months intensive phase	After 6 months of treatment
1	21	>2	41.24 ± 4.12	42.91 ± 3.87**	46.76 ± 3.94**,##	4.05	13.39
2	19	>10	42.21 ± 3.44	43.37 ± 3.75*	47.52 ± 4.12**,##	2.75	12.58

Values are mean ± SD

Tukey HSD post test for repeated measures ANOVA—* $p < 0.05$, ** $p < 0.01$ vs PTB-0; ## $p < 0.01$ vs PTB-2

Table 2 Mean body weight in Groups 1a, 1b, 2a, 2b pulmonary tuberculosis patients at diagnosis (PTB-0), at 2 months post treatment (PTB-2) and 6 months post treatment (PTB-6)

Groups	No. of patients	PCT (ng/ml)			Body weight (kgs)			Mean percentage gain in body weight	
		PTB-0	PTB-2	PTB-6	PTB-0	PTB-2	PTB-6	After 2 months intensive phase	After 6 months of treatment
1a	5	>2	>2	<2	43.2 ± 4.97	45.2 ± 4.03*	48.8 ± 5.36**,##	4.63	12.96
1b	16	>2	>10	<2	40.63 ± 3.79	42.19 ± 3.66*	46.13 ± 3.34**,##	3.84	13.54
2a	3	>10	>2	<2	44 ± 2.65	45.33 ± 2.52	50 ± 3.46**,##	3.02	13.64
2b	16	>10	>10	<2	41.88 ± 3.54	43 ± 3.88	47.06 ± 4.16**,##	2.67	12.37

Values are mean ± SD

Tukey HSD post test for repeated measures ANOVA—* $p < 0.05$, ** $p < 0.01$ vs PTB-0; ## $p < 0.01$ vs PTB-2)

of treatments, with respect to body weight at diagnosis, were then compared between the two groups.

Results

The mean body weights of Groups 1 and 2 at PTB-0, PTB-2 and PTB-6 are shown in Table 1. In both groups, mean body weights at PTB-2 and PTB-6 were significantly higher than those at PTB-0. Mean body weights at PTB-6 were significantly higher than those at PTB-2. However, percentage body weight gain following 2 months of intensive treatment was higher in group 1 (4.05 % gain, $p < 0.01$ for PTB-2 vs PTB-0) than in group 2 (2.75 % body weight gain, $p < 0.05$ for PTB-2 vs PTB-0). Thus, although body weights were gradually increasing in both groups during the course of treatment, the percentage weight gain in group 1 was tending more towards the desirable minimum gain of 5 % during intensive phase. It was observed that serum PCT at the end of 6 months of treatment had dropped down to <2 ng/ml in all patients. However, at the end of 2 months of intensive phase of treatment, the prohormone had decreased in some patients and had further increased in some. Accordingly, we divided the study groups into two sub groups each—Group 1a ($n = 5$; patients of group 1 with serum PCT > 2 ng/ml at PTB-2), Group 1b ($n = 16$; patients of group 1 with serum

PCT > 10 ng/ml at PTB-2); Group 2a ($n = 3$; patients of group 2 with serum PCT > 2 ng/ml at PTB-2) and Group 2b ($n = 16$; patients of group 2 with serum PCT > 10 ng/ml at PTB-2). Table 2 shows the body weights of Groups 1a, 1b, 2a, 2b at PTB-0, PTB-2 and PTB-6. In both sub groups of group 1, body weight gain following intensive phase of treatment was significant when compared to the weights at diagnosis ($p < 0.05$ in both groups for PTB-2 vs PTB-0). However, the mean body weight of group 1a at the end of intensive phase tended more towards the desirable weight gain of 5 % than did the mean body weight of group 1b (4.63 % gain in 1a, 3.84 % gain in 1b). As shown in Table 2, body weights in both the subgroups of group 2 at the end of 2 months of chemotherapy were not significantly different from those at diagnosis. In terms of percentage weight gain, group 2a showed a gain of 3.02 % and group 2b showed a gain of 2.67 %. At the end of 6 months of treatment, body weight gain was very significant in all four groups when compared to the weights at diagnosis ($p < 0.01$ for PTB-6 vs PTB-0) or at the end of intensive phase of therapy ($p < 0.01$ for PTB-6 vs PTB-2).

Discussion

Malnutrition is common among TB patients, with prevalence estimates ranging from 21 % in Peru to 61 % in

Malawi and 62 % in Uganda [13–15]. Most TB patients experience substantial weight gain during TB treatment [16–18]. Reported average weight gain during TB treatment includes 4.9 kg in Indonesia, 5.7 kg in Guinea-Bissau, and 6.9 kg in Tanzania [16–19]. According to Khan et al. [10], a weight gain of 5 % or less during the first 2 months of therapy is associated with an increased risk of relapse, even after controlling for other risk factors for relapse. In the present study, although body weights were gradually increasing in both groups during the course of treatment, the percentage weight gain in group 1 was tending more towards the desirable minimum gain of 5 % during intensive phase. Noteworthy is the observation that in group 1, the disease-induced increase in serum procalcitonin (PCT) was less than that in group 2. One very recent study attributes an anorectic effect to amino-PCT (N-PCT), the biologically active fragment of PCT. It has been shown that administration of N-PCT to free-feeding, freely moving unstressed rats significantly reduced food intake in a dose-dependent manner and decreased body weight gain [11]. In the present study, body weight gain during intensive phase tended more towards the desirable gain of 5 % in the study group with a lower increase in serum PCT than in the group with a higher increase in the prohormone. Further studies are needed to confirm whether increased serum PCT reflects increased central N-PCT activity on feeding behavior or whether peripherally derived PCT and its bioactive fragment N-PCT enter the CNS via a yet to be elucidated mechanism, to regulate feeding behaviour. Duplication of the present research with randomized controlled trials and involving a quantitative estimation of serum PCT need to be conducted. The small sample size and lack of correlational analysis between serum PCT and body weight changes due to the semi-quantitative nature of serum PCT estimation, is a limitation of the present study. Hence, future studies with a quantitative estimation of serum PCT would be more helpful in determining correlation coefficients between serum PCT and body weights in pulmonary tuberculosis before and after treatment.

A detailed discussion on alterations in serum PCT in PTB patients during and after treatment has already been done in an earlier study by the present authors [8] and hence, this aspect shall not be discussed here. The present authors are aware that serum PCT in 19 out of 40 patients at PTB-0 and in 32 out of 40 patients at PTB-2 was >10 ng/ml, a level which, by current guideline of outcome set by B.R.A.H.M.S, is indicative of sepsis. However, all patients were clinically stable and none of them were reported to go into sepsis but on the other hand, were clinically responding to treatment, as shown by their sputum conversion at the end of 2 months. Also, hepatic profile of the patients did not reflect any significant liver

damage. Hence, liver damage as a reason for the high increase in serum PCT is also ruled out. Keeping in mind that the analysis was semi quantitative and had its own limitations, the authors plan to repeat the present study with a quantitative kit for PCT estimation.

In the present study, another finding was that percentage body weight gain during treatment seemed to be determined more by serum PCT levels at diagnosis than by serum PCT levels at the end of intensive phase of treatment. There was significant body weight gain in both the subgroups of group 1 (where serum PCT > 2 ng/ml at diagnosis) but no significant body weight gain in both the subgroups of group 2 (where serum PCT > 10 ng/ml at diagnosis), at the end of intensive phase of treatment. Indeed, body weight gain in group 1a tended more towards the desirable weight gain of 5 % than in group 1b at the end of intensive phase. However, although in group 1b serum PCT increased and in group 2a the prohormone decreased at the end of intensive phase, percentage body weight gain in group 1b was better than in group 2a. Tavares et al. [11] mention in their study that the anorectic effect of N-PCT was extremely potent at even low doses but comparatively less significant at the highest dose. Their study suggests that the central receptors mediating N-PCTs anorectic effect were already fully activated at lower doses. Interestingly, at the end of continuation phase where serum PCT was less than 2 ng/ml in all patients, body weight gain in all groups was more than 12 % as compared to the weights at diagnosis.

Although there has been enough research on the role of PCT as a sepsis marker, the function of PCT in humans is still not fully understood. The present study is in agreement with suggestions by Tavares et al. that PCT is involved in regulation of feeding behavior and energy homeostasis. It provides scope for future research in better understanding the mechanisms responsible for anorexia and weight loss in other conditions, e.g. cachexia in cancer.

Conclusion

Increase in serum PCT levels in pulmonary tuberculosis is inversely associated with body weight gain during treatment. Body weight gain tends more towards the desirable weight gain of 5 % during intensive phase when the increase in serum PCT is less than when it is higher. This indicates that PCT plays a role in regulation of body weight gain in anorectic conditions like tuberculosis. However, further studies are needed with quantitative estimation of serum PCT to establish a statistical correlation between increase in serum PCT levels and body weight gain during treatment of bacterial infections like tuberculosis.

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