Lack of Weight Gain and Relapse Risk in a Large Tuberculosis Treatment Trial

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Background: **Readily identified markers of tuberculosis relapse risk are needed, particularly in resource-limited settings. The association between weight gain or loss during antituberculosis therapy and relapse has not been well studied.**

Methods: **Subjects in the Tuberculosis Trials Consortium Study 22 were studied. Underweight was defined as 10% or more below ideal body weight at diagnosis. Weight change was assessed between (*1*) diagnosis and completion of induction phase therapy, (*2*) diagnosis and end of continuation phase therapy, and (*3*) completion of induction to completion of continuation phase therapy.**

Results: **A total of 857 subjects were monitored for 2 yr, and 61 of 857 (7.1%) relapsed. Relapse risk was high among persons who were underweight at diagnosis (19.1 vs. 4.8%; $p < 0.001$) or who had a body mass index of less than 18.5 kg/m^2 (19.5 vs. 5.8%; $p < 0.001$). Among persons who were underweight at diagnosis, weight gain of 5% or less between diagnosis and completion of 2-mo intensive phase therapy was moderately associated with an increased relapse risk (18.4 vs. 10.3%; relative risk, 1.79, 95% confidence interval, 0.96–3.32; $p = 0.06$). In a multivariate logistic regression model that was adjusted for other risk factors, a weight gain of 5% or less between diagnosis and completion of 2-mo intensive phase therapy among persons underweight at diagnosis was significantly associated with relapse risk (odds ratio, 2.4; $p = 0.03$).**

Conclusions: **Among persons underweight at diagnosis, weight gain of 5% or less during the first 2 mo of treatment is associated with an increased relapse risk. Such high-risk patients can be easily identified, even in resource-poor settings. Additional studies are warranted to identify interventions to decrease risk of relapse in such patients.**

Keywords: body mass index; clinical trial; relapse; tuberculosis; weight

Weight loss and nutritional depletion are often seen in patients with tuberculosis at the time of tuberculosis diagnosis (1–3). Malnutrition appears to increase the risk of developing tuberculosis, particularly in animal models (4). However, cause and effect are difficult to distinguish because tuberculosis disease causes weight loss. Among tuberculin skin-test–positive U.S. Navy recruits, the risk of tuberculosis was nearly fourfold higher among men who were at least 10% underweight at baseline than in men who were at least 10% overweight (5).

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Body mass index (BMI) is a more accurate marker of nutritional status than weight because it also takes height into account. In a study among 1,717,655 Norwegians older than 14 yr who were monitored for 8–19 yr after intake into a radiographic screening program, the relative risk of tuberculosis among persons in the lowest BMI category was more than fivefold higher than the group in the highest BMI category, and it was independent of sex, age, and radiographic findings (6).

Weight gain and other improvements in nutritional indicators after effective chemotherapy for tuberculosis have been reported (2, 3). However, the relationship between changes in weight while receiving antituberculosis therapy and subsequent relapse risk has not been well studied. Easily utilized and inexpensive markers of relapse risk are needed, particularly in the developing world, where resources are limited. Therefore, we examined the association between changes in weight during therapy and relapse risk among patients with tuberculosis in a large, randomized, prospective trial of antituberculosis therapy. Because being underweight at baseline was independently associated with relapse risk in that randomized trial (7), we stratified the study population according to baseline weight. Preliminary results were previously presented in abstract form (8).

METHODS

Study Population

The Tuberculosis Trials Consortium Study 22 was a large, multicenter, randomized, nonblinded study comparing once-weekly isoniazid–rifapentine with twice-weekly isoniazid–rifampin during the continuation phase of treatment for pulmonary tuberculosis in adults (7). Eligibility criteria included age of 18 yr or older, a Karnofsky score of 60 or more, an HIV test within 6 mo, and completion of 8 wk of standard four-drug (isoniazid, rifampin, pyrazinamide, and ethambutol) directly observed treatment. Exclusion criteria included pregnancy or breastfeeding, silicosis or skeletal tuberculosis, or moderate hematologic, renal, or hepatic disease. Patients were monitored for 2 yr after treatment.

This analysis included HIV-seronegative patients only. Subjects were excluded if they failed or died during treatment, did not complete the 2-yr follow-up, or did not have weight and ideal body weight recorded at diagnosis.

Measures

Demographic, socioeconomic, and clinical data were obtained at enrollment, as well as a chest radiograph and sputum smears and cultures.

Body weight (kg) was measured using available scales at diagnosis, at enrollment, monthly during treatment, and every 3 to 6 mo during follow-up. Body weight was measured wearing light clothes. "Diagnosis weight" was the weight at initial diagnosis; "weight at the end of 2-mo intensive phase therapy" was the weight after completion of the first 8 wk of treatment, and "completion weight" was the weight after completing the next 16 wk of treatment.

Height (cm) was assessed in a pharmacokinetic substudy, or obtained later by contacting all sites. BMI was defined as weight in kilograms divided by the square of height in meters (kg/m^2). "Low BMI" was a BMI of less than 18.5 (9, 10). "Underweight" was defined as 10% or more below ideal body weight at diagnosis using Metropolitan Life

table data for medium frame–size individuals stratified by sex and height (7).

Laboratory Methods

Initial isolates of *Mycobacterium tuberculosis* and isolates from any cultures positive after therapy underwent genotyping by IS*6110*-based restriction fragment length polymorphism analysis using the standardized method (11), as described previously (12).

Definitions

Patients who completed treatment and remained relapse-free during follow-up were termed "cure"; those who had sputum culture(s) positive for *M. tuberculosis* after treatment were termed "relapse." The definition of relapse required that the *M. tuberculosis* isolate of the initial and recurrent tuberculosis episode match by DNA fingerprinting. Weight changes were calculated as the differences between weights measured at the following intervals: (*1*) at tuberculosis diagnosis and the end of 2-mo intensive phase therapy, (*2*) at diagnosis and the end of continuation, and (*3*) at the end of 2-mo intensive phase therapy and the end of continuation. Percentage of weight change was calculated as the difference in weights at the two times divided by the weight at the earlier time, multiplied by 100. We used a three-level risk factor variable developed from Study 22 data for the 2003 American Thoracic Society recommendations for tuberculosis treatment (13): 0 for patients who had neither cavitary disease nor positive sputum culture, 1 for patients who had either cavitary disease or positive sputum culture, and 2 for patients who had both cavitary disease and positive sputum culture after 2 mo of treatment. Patients with either cavitary disease or a positive 2-mo culture were combined since their clinical outcomes were similar (13).

Statistical Analysis

Means, standard deviations, and frequency distributions of clinical and demographic characteristics were calculated. Comparisons between outcome categories (cure and relapse) were performed using a two-sample *t* test or Wilcoxon rank-sum test for continuous variables and χ^2 or Fisher's exact test for categoric variables. Logistic regression was used to model multivariate relationships of percentage of weight gain ($\leq$ 5 vs. $>$ 5%), controlling for sex, age, and the interaction between sex and age, and stratified by weight category at diagnosis. All statistical analyses were performed using SAS for Windows version 8 (SAS Institute, Cary, NC).

RESULTS

Of the 1,004 HIV-seronegative patients who enrolled in the study, 922 successfully completed tuberculosis treatment and provided treatment outcome information (cure or relapse); 82 patients either did not complete follow-up (n = 76) or could not be assessed for relapse (n = 6). Of the 922 subjects that completed treatment, 65 did not have a weight recorded at diagnosis, leaving 857 subjects for the analysis. The 147 excluded patients did not differ from study patients with respect to demographic or clinical factors (including weight and BMI), except that excluded patients were more likely to have a positive sputum culture after 2 mo of treatment (33 vs. 19%; $p < 0.001$). Of the 857 subjects, 273 did not have a height available with which to calculate BMI. Characteristics of those with and without BMI are shown in Table 1. Subjects without a recorded height were more likely to be homeless; in all other respects, the groups were comparable. There was no evidence of heterogeneity among patients enrolled from the different study sites.

During follow-up, 61 (7.1%) of 857 patients relapsed. Consistent with results reported in the parent study (7), the relapse rate was higher among persons randomized to rifapentine than those who received rifampin (40/432 [9.3%] vs. 21/425 [4.9%]; $p = 0.01$). After stratifying by whether or not persons were underweight at diagnosis, relapse rates were not significantly different by treatment arm in those who were underweight (n = 261 [Table 2]: 25/138 [18.1%] in rifapentine arm vs. 12/123 [9.8%] in rifampin arm; $p = 0.06$) and those who were not underweight (n = 596 [Table 2]: 15/294 [5.1%] in rifapentine arm vs. 9/302 [3.0%] in rifampin arm; $p = 0.19$). Therefore, persons in both study arms were combined for the analysis of weight change on relapse risk.

TABLE 1. COMPARISON OF STUDY SUBJECTS (n = 857) WITH AND WITHOUT AVAILABLE BODY MASS INDEX

Characteristic	BMI Available		p Value
	Yes (*n = 584*)	No (*n = 273*)	
Male	438 (75.0%)	200 (73.3%)	0.59
White race	105 (18.0%)	60 (16.9%)	0.69
Pulmonary TB	559 (95.2%)	266 (97.4%)	0.22
Homeless/living in a shelter $\geq$ 6 mo	93 (15.9%)	64 (23.4%)	0.008
Alcohol use ($\geq$ 1 drink/d)	249 (42.7%)	126 (46.2%)	0.34
Illicit drug use (any time in prior 5 yr)	122 (20.9%)	53 (19.4%)	0.62
In prison ($\geq$ 1 mo in prior 5 yr)	58 (9.9%)	31 (11.4%)	0.52
Culture positive at 2 mo	105 (19.6%)	39 (16.3%)	0.27
Cavitary disease	303 (53.7%)	139 (52.1%)	0.65
Rifapentine treatment arm	298 (51.0%)	134 (49.1%)	0.60
Age (mean, SD), yr	43.6 $\pm$ 14.7	45.2 $\pm$ 15.6	0.15
Weight at TB diagnosis, kg (baseline)	61.2 $\pm$ 13.5	61.4 $\pm$ 12.1	0.82

Definition of abbreviations: BMI = body mass index; TB = tuberculosis.

Median weight at diagnosis was significantly lower in persons who relapsed than in those who did not: 55.8 kg (interquartile range [IQR], 50.8–64.0) for relapsed patients, and 59.0 kg (IQR, 52.2 – 68.0) for those who did not relapse ($p = 0.047$). Median BMI was also lower: 18.3 (IQR, 17.3–20.8) for relapsed patients and 20.6 (IQR, 18.8 – 23.3) for cured patients ($p < 0.0001$).

Comparison of the association between body weight category or BMI and relapse risk for the 584 subjects with both BMI and weight available is shown in Table 3. Underweight patients had significantly higher relapse rates than those with normal weight at tuberculosis diagnosis (relative risk [RR], 3.99; 95% confidence interval [95% CI], 2.30–6.76; $p < 0.001$). A similar relationship was found between patients with a BMI of 18.5 or less (30/154; 19.5%) compared with those with a BMI greater than 18.5 (25/430; 5.8%; RR, 3.92; 95% CI, 2.22–6.91; $p < 0.001$). As seen in Table 3, altering the BMI cut-off did not improve the ability to predict relapse compared with ideal weight category. Therefore, given the larger sample size, ideal weight category was used to stratify patients when assessing weight gain on tuberculosis treatment.

Table 2 shows the relationship between weight gains of 5% or less compared with weight gain of greater than 5% during the three treatment periods. Weight gain was examined both as an absolute number of pounds gained (data not shown) and as a percentage. Ten subjects did not have a weight recorded at the end of treatment. Therefore, only 847 subjects could be evaluated for the periods of diagnosis to the end of 6 mo and the end of 2-mo intensive phase therapy to 6 mo. Overall, weight gain of 5% or less during any of the three time periods examined was not associated with relapse. However, in the subgroup of patients who were underweight at diagnosis, the association of relapse with failure to gain at least 5% of body weight between diagnosis and the completion of 2-mo intensive phase therapy approached statistical significance (RR, 1.79; 95% CI, 0.96–3.32; $p = 0.06$).

As previously reported, other characteristics that were significantly associated with relapse in these patients included cavitary disease on chest X-ray and a positive 2-mo sputum culture (7). Therefore, we examined the additional predictive value of weight gain when added to either cavity or positive 2-mo culture

TABLE 2. RELAPSE RATE STRATIFIED BY IDEAL BODY WEIGHT CATEGORY AND TUBERCULOSIS TREATMENT TIME PERIOD

		TB Treatment Time Period		
⩾ 10% below Ideal Body Weight at Diagnosis	Weight Change during TB Treatment Period	Diagnosis to End of 2-mo Intensive Phase (*relapse/total*)	Diagnosis to End of Continuation Phase (*relapse/total*)	End of 2-mo Intensive Phase to End of Continuation Phase (*relapse/total*)
Yes	⩽ 5.0%	23/125 (18.4%)*	8/53 (15.1%)	17/137 (12.4%)
	> 5.0%	14/136 (10.3%)	29/205 (14.1%)	20/121 (16.5%)
	Total	37/261 (14.2%)	37/258 (14.3%)	37/258 (14.3%)
No	⩽ 5.0%	15/376 (4.0%)	7/231 (3.0%)	12/386 (2.9%)
	> 5.0%	9/220 (4.1%)	17/358 (4.7%)	12/203 (5.9%)
	Total	24/596 (4.0%)	24/589 (4.1%)	24/589 (4.1%)
Total	⩽ 5.0%	38/501 (7.6%)	15/284 (5.3%)	29/523 (5.5%)
	> 5.0%	23/356 (6.5%)	46/563 (8.2%)	32/324 (9.9%)
	Total	61/857 (7.1%)	61/847 (7.2%)	61/847 (7.2%)

Definition of abbreviation: TB = tuberculosis.

* p = 0.06 compared with group with weight change > 5.0%. None of the other comparisons between persons gaining ⩽ 5% versus > 5% were statistically significant.

or both. Of the 857 subjects, 103 had missing information about cavity or culture result at 2 mo, so the total number of subjects in this analysis was 754. The association of weight gain between diagnosis and the end of 2-mo intensive phase therapy and relapse risk, stratified by the number of concomitant risk factors, is shown in Table 4. The difference in percentage of weight gain was statistically significant only in underweight persons with both cavitary disease and positive 2-mo culture (RR, 2.7; 95% CI, 1.1–6.5; p = 0.02).

The predictive power of sputum smear at diagnosis and after 2 mo of treatment, in conjunction with baseline weight and weight change during the 2-mo intensive phase of treatment, was also assessed (*see* the online supplement).

If only weight change between diagnosis and end of 2-mo intensive phase therapy was assessed among persons underweight at diagnosis, the relapse risk was 11.9% among persons gaining more than 5% body weight versus 20.3% in persons gaining 5% or less; the relapse risk was 4.2% among the 523 persons who were not underweight at baseline (Table 4). The 37 relapses among those underweight at baseline accounted for 63% of all relapses (n = 59; Table 4).

The risk of relapse attributable to weight gain between diagnosis and the end of 2-mo intensive phase therapy, stratified by weight category at diagnosis and adjusted for other risk factors for relapse, sex, age, and the interaction between sex and age, is shown in Table 5. Among persons underweight at baseline, weight gain of 5% or less was independently associated with relapse (odds ratio, 2.4; p = 0.03).

Although steroids can cause weight gain and therefore could potentially affect relapse risk, only 22 (2.6%) of the 857 study patients received steroids during antituberculosis therapy. Of the 22, only 1 relapsed.

TABLE 3. RELAPSE RATE BY BODY MASS INDEX CATEGORY AND BY IDEAL BODY WEIGHT CATEGORY AT DIAGNOSIS

	⩾ 10% below Ideal Body Weight			
BMI Category	Yes (*relapse/total*)	No (*relapse/total*)	p Value	Total
⩽ 18.50	29/130 (22.3%)	1/24 (4.2%)	0.048	30/154 (19.5%)
18.51–19.00	3/15 (20.0%)	0/13 (0.0%)	0.23	3/28 (10.7%)
19.01–25.00	4/43 (9.3%)	15/270 (5.6%)	0.31	19/313 (6.1%)
⩾ 25.51	0/0 (0.0%)	3/89 (3.4%)	—	3/89 (3.4%)
Total	36/188 (19.1%)	19/396 (4.8%)	< 0.001	55/584 (9.4%)

Definition of abbreviation: BMI = body mass index.

DISCUSSION

The most notable finding of this study was that among persons who were initially underweight (defined as ⩾ 10% below ideal body weight), those who had more than 5% weight gain during the 2-mo intensive phase of therapy had a lower relapse risk than those who gained 5% or less (10.3 vs. 18.4%; p=0.06). This association still held among underweight persons with a cavity on chest radiograph and positive sputum culture after 2 mo of antituberculosis treatment (18.5% relapse in persons with > 5% weight gain during the 2-mo induction phase vs. 50.5% relapse in persons with < 5% weight gain; p = 0.02). The association also persisted in a multivariate analysis that controlled for sex, age, race, treatment arm, cavity on chest radiograph, and positive sputum culture after 2 mo of antituberculosis treatment. This finding extends those of the parent study, which focused just on baseline weight, rather than on weight change with therapy (7).

It is unclear whether persons are at increased relapse risk if they do not gain weight during 2-mo intensive therapy, or whether they are at increased relapse risk because they do not gain weight. Less than 5% weight gain could be a marker of increased tuberculosis disease activity and/or poor response to therapy. This finding also has unclear clinical applications. Should every effort be made to have underweight patients undergo more than 5% weight gain during the first 2 mo of therapy, or should additional interventions (e.g., extend duration of antituberculosis treatment) be made to decrease relapse risk in underweight patients who do not have greater than 5% weight gain? Perhaps both interventions are indicated. The very high relapse rate (50.5%) among underweight persons with a cavity on chest radiograph, positive sputum culture after 2 months of antituberculosis treatment, and 5% or less weight gain during 2-mo intensive phase therapy raises the possibility that such patients should receive therapy that is either more intensive or of greater duration. Conversely, the 0.6% relapse rate among persons without any of these risk factors suggests that they could possibly receive a shorter duration of therapy. Neither of these questions was addressed in this study, but they should be addressed in randomized, controlled trials.

There are several limitations to this study. First, all study patients were participants in a clinical trial of antituberculosis

TABLE 4. EFFECT OF BASELINE WEIGHT, CAVITY, AND CULTURE STATUS AT 2 mo ON ASSOCIATION BETWEEN WEIGHT CHANGE AND RELAPSE

		Risk Factors			
⩾ 10% below Ideal Body Weight	Weight Change during 2-mo Intensive Phase	None (*relapse/total*)	Cavity or Positive 2-mo Culture (*relapse/total*)	Cavity and Positive 2-mo Culture (*relapse/total*)	Total (*relapse/total*)
Yes	⩽ 5.0%	1/36 (2.8%)	10/53 (18.9%)	12/24 (50.5%)*	23/113 (20.3%)
	> 5.0%	3/35 (8.6%)	6/56 (10.7%)	5/27 (18.5%)	14/118 (11.9%)
	Total	4/71(5.6%)	16/109 (14.7%)	17/51 (33.3%)	37/231 (16.0%)
No	⩽ 5.0%	1/164 (0.6%)	7/136 (5.1%)	5/35 (14.3%)	13/335 (3.9%)
	> 5.0%	2/87 (2.3%)	1/76 (1.3%)	6/25 (24.0%)	9/188 (4.8%)
	Total	3/251 (1.2%)	8/212 (3.8%)	11/60 (18.3%)	22/523 (4.2%)
Total	⩽ 5.0%	2/200 (1.0%)	17/189 (9.0%)	17/59 (28.8%)	36/448 (8.0%)
	> 5.0%	5/122 (4.1%)	7/132 (5.3%)	11/52 (21.2%)	23/306 (7.5%)
	Total	7/322 (2.2%)	24/321 (7.5%)	28/111 (25.2%)	59/754 (7.8%)

* p = 0.02 compared with group with weight change > 5.0%. None of the other comparisons between persons gaining ⩽ 5% versus > 5% were statistically significant.

therapy, and had to receive 2 mo of treatment before entry to qualify for the study. Patients were eligible only if they had no severe underlying medical condition. Thus, study patients did not reflect the population of all patients with tuberculosis, which limits generalizability. However, the study population was intentionally selected to favor persons with the greatest likelihood of completing therapy and surviving 2 yr after completion so that relapse risk could be evaluated. Second, height was not available for 273 of 857 study patients—32% of the patients included in this analysis. This limited the number of patients for whom BMI could be assessed as a predictor of relapse, and also decreased statistical power. However, the clinical and demographic characteristics of the persons in whom BMI could be calculated did not differ substantially from those in whom BMI could not be calculated. Third, weight change was assessed over several intervals, raising the issue of multiple comparisons and the possibility that statistically significant associations were due to chance. However, there is biological plausibility that weight change during the first 2 mo of treatment would have the greatest impact on relapse risk. The combination of isoniazid, rifampin, and pyrazinamide that all patients received during the first 2 mo of treatment dramatically decreases the burden of *M. tuberculosis* (14). All three drugs play an important role during this initial 2 mo of treatment, but particularly pyrazinamide, which is a sterilizing drug, and is active (and therefore given) only during the first 2 mo of treatment (15). Treatment during the last 4 mo of therapy is focused on substantially fewer *M. tuberculosis* organisms, which replicate more slowly. Finally, the 147 patients excluded from the study were more likely to have a positive sputum culture after 2 mo of treatment, and were therefore at higher risk of relapse, than those included in the study. Although this could have influenced the study results, it should be noted that there was no difference in weight or BMI among excluded versus included patients.

Strengths of the study include its large size, prospective design, active follow-up for relapse, and longitudinal monitoring of weight from treatment initiation through 2 yr after completion of therapy.

We conclude that, among persons who are underweight at diagnosis, weight gain of 5% or less during the first 2 mo of therapy is associated with an increased risk of relapse, even after controlling for other risk factors for relapse. In the absence of data on other predictors of relapse, weight at diagnosis and weight change after the 2 mo of intensive phase treatment can help identify persons at high risk of relapse. This is particularly important for the developing world, where resources are limited and chest radiographs and sputum cultures cannot always be obtained. Additional studies are warranted to better define the underlying mechanism of this association, and to identify interventions that decrease relapse risk.

TABLE 5. RISK FACTORS FOR TUBERCULOSIS RELAPSE, ADJUSTING FOR SEX, AGE, AND INTERACTION OF SEX AND AGE

	Stratified Group			
	Underweight		Not Underweight	
Variable	OR (*95% CI*)	p Value	OR (*95% CI*)	p Value
⩽ 5% weight gain*	2.4 (1.1–5.5)	0.03	1.0 (0.4–2.6)	0.96
Cavity and sputum culture + after 2 mo of treatment†	7.9 (2.2–28.4)	0.02	17.8 (4.7–68.0)	< 0.0001
Cavity or sputum culture + after 2 mo of treatment†	3.5 (1.0–12.1)	0.05	3.1 (0.8–12.1)	0.10
Rifapentine treatment arm	2.0 (0.9–4.4)	0.10	1.3 (0.5–3.2)	0.59
White race	2.9 (1.3–6.7)	0.01	1.5 (0.5–4.7)	0.48

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

Multivariate logistic regression analysis. Results are stratified according to whether or not patients were ⩾ 10% below ideal body weight (underweight) at diagnosis.

* Between diagnosis and completion of 2-mo intensive phase therapy.

† Compared with persons with no cavity on chest radiograph and negative sputum culture after 2 mo of treatment.

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