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Effect of Nutritional Support on Treatment of Multi-Drug Resistant Tuberculosis in Rajshahi Division, Bangladesh

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Abstract

Introduction: Multi-drug resistant tuberculosis (MDR-TB) is a public health crisis throughout the world including Bangladesh particularly due to its complexities in diagnosis, longer treatment regimen, and adverse drug reaction. Nutritional supplementation has significant impact on patient's weigh gain and optimum weight gain is a biomarker of treatment response. The objective of this study was to measure body mass index (BMI) progress among MDR-TB patients in different phases of treatment. **Methodology:** A prospective observational study was conducted from March 2010 to July 2015 in Chest Disease Hospital (CDH), Rajshahi and different communities of Rajshahi Division, Bangladesh. A total of 233 confirmed MDR-TB patients were selected from CDH who received treatment and nutritional support from ongoing national TB control program (NTP). They received free diagnosis, follow up tests, treatment and nutritional support as regular diet as well as cash amount Bangladeshi taka (BDT.) 1000 per month in CDH. Along with treatment, they also received only cash amount BDT. 1500 per month as nutritional support at community level. Weight measurement was taken at regular interval from enrollment to completion of treatment. Chi-square, paired t-test and linear regression analysis were used in this study. **Results:** The baseline prevalence of undernourished (BMI < 18.5 kg/m^2) was 82.4%. After two months of treatment, 14.5% underweight patients gained weight and reverted to normal BMI. Regression analysis showed the decreasing tendency of BMI progress with increasing age which was significant among male patients ($p < 0.05$). We observed reversely that patients gained more BMI in intensive phase than continuation phase of treatment. The cohort results demonstrated that the

treatment success rate was lower (<83%) among initially underweight patients than their counterparts (>92%). **Conclusion:** Nutritional support has synergistic effect on treatment response. Adequate nutritional support with proper treatment would help to get better outcomes particularly at community level. Gender issue should also be addressed at household level.

Keywords

Bangladesh, BMI Progress, MDR-TB, Nutritional Support

1. Introduction

Multi-drug resistant tuberculosis (MDR-TB) is a major obstacle for TB control due to difficulties in diagnosis, longer treatment regimen and more adverse drug reaction [1] [2]. The drug susceptible tuberculosis (DS-TB) is the main source of MDR-TB due to irregular or inadequate treatment following poor adherence, supply interruption or physicians error or treated with wrong drugs [3] [4]. Along with cough, fever and anorexia, weight loss is a major feature of both TB and MDR-TB [3] [5] [6]. A MDR-TB patient usually faces more loss of appetite which causes more weight loss [3] [5]. A marked under nutrition is an identified risk factor for TB related mortality [7] [8]. Studies perceived that malnourished are more prone to develop TB and they are more likely to have advanced disease and greater risk of side effects and deaths compared to patients with normal BMI [9] [10]. There is synergistic relationship between TB and malnutrition adversely impact of each other [11] [12]. Weight gain over time during treatment can be a biomarker of treatment effectiveness and better treatment outcomes [3] [8]. It is a simple and less expensive but valuable tool for patient management. The early screening of malnutrition and nutritional supplementation can effectively response to treatment and rapid recovery from disease [13] [14]. Study suggests that along with treatment, supplementation of nutrition particularly among malnourished patients (BMI < 18.5 kg/m^2) with dietary counseling would be a good practice [15]. The correction of malnutrition can reduce suffering, costs, and deaths and increase weight [16]. In Bangladesh, poverty, population density and malnutrition are common which reduces productivity in adults, increases susceptibility to infection, and decelerates recovery from illness [17] [18]. In addition, malnutrition enhances the reactivation of TB disease, and conversely, patients become malnourished when they contract the disease [18] [19] [20]. Bangladesh ranks 6^{th} among 22 high DS-TB and 9^{th} among 25 high MDR-TB burden countries [3] [21] [22]. Bangladesh National Tuberculosis Control Program (NTP) is providing nationwide free diagnostic and treatment support and other necessary support including nutritional support to MDR-TB patients under programmatic management of drug resistant TB (PMDT) [5]. However, once diagnosed as MDR-TB in north-west belt of Bangladesh, patients were admitted to Chest Disease Hospital (CDH), Rajshahi. They stayed for a full period

of intensive phase of treatment. After completion of four months intensive phase, they moved to the community to continue the continuation phase of treatment under PMDT following discharge criteria. It is noted that MDR-TB patients were receiving food and financial support in both hospital and the community through PMDT. The purpose of this study was to evaluate the effect of nutritional support at different phases of treatment.

2. Methodology

2.1. Study Design and Site

An observational prospective study was conducted at Chest Disease Hospital (CDH), Rajshahi and at home level during March 2010 to July 2015. Two hundred and thirty three confirmed adult MDR-TB patients were included in the study. The study purpose was shared and informed consent was taken from each respondent. After completion of measurement and other relevant data, we waited for additional fifteen months to get treatment outcomes report as cohort results.

2.2. Inclusion Criteria

Out of 340 registered MDR-TB patients at CDH under PMDT, 233 patients (68%) were selected for this study who had a complete cohort record. Finally, we analyzed BMI progress of 187 patients (55%) who had regular weight records from the beginning to the end of treatment.

2.3. Exclusion Criteria

Patients were excluded from the study if: 1) transfer out, 2) a major defaulter within one month, 3) primarily detected mono and poly drug resistant TB, 4) Drug susceptible TB cases and 5) Patient below 15 years old. For BMI, the rest of patients were excluded for their irregular weight records and residence other than Rajshahi Division. HIV status was unknown. We assessed the effect of nutritional support to adult MDR-TB patients on the basis of BMI variation with treatment and food support at regular interval started from hospital and ended to community. In this study, the optimum BMI gain indicates the treatment effectiveness as well as nutritional effect. The gradual BMI gain indicates the recovery process from disease with adequate nutrition. Static BMI indicates recovery process with improper nutrition and decreasing BMI indicates unidentified co-morbidity with improper nutrition or disease with other confounding factors.

2.4. Study Setting

Under the NTP, a special program named as programmatic management of drug resistant TB (PMDT) through which NTP is providing nutritional support to MDR-TB patients at both hospital and community level. The nutritional support was a provision of lunch and dinner at CDH, which comprised of rice vegetables, meat/fish, and lentil soup. In addition, patients received an egg, 250 ml

milk/one banana and pieces of bread as breakfast in the intensive phase of treatment at hospital. Along with free food, diagnosis, follow up tests and treatment, cash support of BDT. 1000 (about US Dollar 12) per month was provided to buy additional food as per patient's choice up to four months of intensive phase. Only the weight progress was measured during the treatment period in different settings and no additional nutritional support was added. However, when the patients moved to the community, based on discharge criteria, BDT. 1500 was given monthly for purchasing food as nutritional support up to completion of treatment under PMDT. In our study area, nine months treatment regimen with four months intensive and five months continuation phases was followed. It is noted that NTP was following 20 to 22 months of treatment regimen for MDR-TB throughout the country except CDH Rajshahi and few other facilities collaborated with non-government organization (NGO)—Damien Foundation [5].

2.5. Data Collection

Socio-demographic and anthropometric data were collected by trained data collectors. The height and weight records were collected during enrollment and subsequently weight was taken monthly up to nine months. All treatment outcomes were collected from the prescribed format and registers of CDH.

2.6. Outcome Variable

BMI was considered as outcome variable which was calculated from height and weight using the formula, BMI = weight in (kg)/height in (meter)^2. According to WHO standard, four categories of BMI-underweight (BMI < 18.5 kg/m^2), normal (18.5 ≤ BMI < 25 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) was followed [23].

2.7. Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS, IBM version 23) software. Chi-square test was used to find out the association between two categorical variables. As outcome variables (BMI) were normally distributed, paired sample t-test was utilized to see the difference between two phases of treatment and linear regression analysis was performed to measure the weight gain over time according to gender. The p-value < 0.05 was considered as statistically significant.

3. Results

Out of 233 respondents for treatment outcomes, 187 patients were eligible for BMI analysis (**Figure S1**). During enrollment, 82.4% patients were underweight and the mean BMI was 16.56 kg/m^2. More than 71% were male patients. Most of the patients (72%) were young age (16 - 37 years) group. The overall treatment success rate was 84.1%. The treatment success rate is the positive treatment out-

comes of combination of cured and treatment completed. A patient is considered as cured when he or she completed treatment according to NTP protocol without evidence of treatment failure and three consecutive sputum cultures are negative with clinical improvement [5]. Subsequently, the technical term treatment completed means the person who completed treatment following NTP protocol but fails to meet the definition of cure due to lack of bacteriological results [5]. In this study, the treatment success rate was also lower among initially underweight patients (82.3%) than normal and overweight patients (92.6%) (**Table 1**). Alternatively, the unsuccessful outcomes such as loss to follow up, death and treatment failure were higher among initially underweight (BMI < 18.5) patients (7.8%, 8.9%, 1.0%) respectively. The term treatment failure of

Table 1. Age and gender distribution according to BMI and treatment outcomes analysis.

Age group	**N (%), n = 187**
16 - 26	79 (42.2)
27 - 37	56 (29.9)
38 - 48	26 (13.9)
≥49	26 (13.9)
Gender	
Male	133 (71.1)
Female	54 (28.9)
Overall Treatment outcomes (TO)	**N (%), n = 233**
Treatment completed	4 (1.7)
Cured	192 (82.4)
Loss to follow up	16 (6.9)
Died	19 (8.2)
Treatment Failure	2 (0.9)
TO among underweight patient	**N (%), n = 192**
Treatment completed	3 (1.6)
Cured	155 (80.7)
Loss to follow up	15 (7.8)
Died	17 (8.9)
Treatment Failure	2 (1.0)
TO among normal, over weight and obese patient	**N (%), n = 41**
Treatment completed	1 (2.4)
Cured	37 (90.2)
Loss to follow up	1 (2.4)
Died	2 (4.9)
Treatment Failure	0 (0.0)

(N: number of patient, there was no "not evaluated and transfer out cases" for outcomes).

MDR-TB depends on follow up tests results. If the sputum is still positive for bacilli in continuation phase (non-conversion) or bacteriological reversion (negative to positive) in continuation phase or evidence of resistance to fluoroquinolones and second line injectable anti-TB drugs are usually considered as treatment failure [5]. The other technical terms are properly described in national PMDT guidelines [5].

After two months of treatment, underweight reduced from 154 (82.4%) to 127 (67.9%). Chi-square test (χ^2) revealed that the underweight reduction rate was higher among male (65.4%) than females (74.1%). Finally, 57 (30.5%) underweight patients gained normal BMI at month nine (Table 2).

The increasing tendency of mean BMI with respect to times was observed and the monthly variation in BMI was explained by 95.2% using polynomial of degree two models (Figure 1). The linear regression analysis demonstrated that the progress of BMI was significantly ($p < 0.05$) declined with increased age among male patients (95% CI −0.036 to −0.003) and among female MDR-TB patients, the BMI progress was also declined with increased age which was not significant (95% CI −0.040 to 0.034) ($p > 0.05$) (Table 3).

Table 2. Body mass index (BMI) changes over time according to gender.

Gender	BMI category	Number of patient (%)	N.P after two months of tr. (%)	N.P after four months of tr. (%)	N.P after six months of tr. (%)	N.P after nine months of tr. (%)
Male MDR-TB	Underweight	109 (81.9)	87 (65.4)	77 (57.9)	77 (57.9)	62 (46.6)
	Normal	23 (17.3)	45 (33.8)	54 (40.6)	54 (40.6)	67 (50.4)
	Overweight	1 (0.8)	1 (0.8)	2 (1.5)	1 (0.8)	4 (3.0)
	Obese	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Female MDR-TB	Underweight	45 (83.3)	40 (74.1)	38 (70.4)	41 (75.9)	35 (64.8)
	Normal	09 (16.7)	14 (25.9)	16 (29.6)	13 (24.1)	19 (35.2)
	Overweight	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Obese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

(N.P: Number of Patient; tr.: treatment).

Table 3. BMI (kg/m^2) progress with age of respondents (regression analysis).

Progress of BMI (kg/m^2) among MDR-TB with patient's age							
	Variable	Coefficient (B)	SE	T-value	P-value	95.0% CI for B	
						Lower Bound	Upper Bound
Total	Respondents' age	−0.018	0.007	−2.408	0.017	−0.033	−0.003
	Constant	2.480	0.263	9.443	0.000	1.962	2.998
Male	Respondents' age	−0.019	0.009	−2.275	0.025	−0.036	−0.003
	Constant	2.495	0.318	7.842	0.000	1.866	3.125
Female	Respondents' age	−0.003	0.018	−0.152	0.880	−0.040	0.034
	Constant	2.140	0.546	3.921	0.000	1.045	3.234

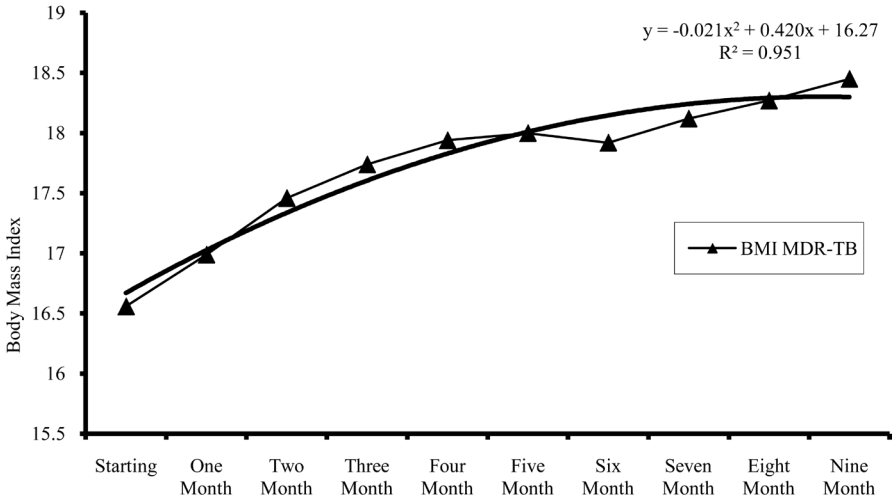

Figure 1. Trend of mean BMI progress among MDR-TB patients with treatment. A polynomial of degree two models among MDR-TB (n = 187, at 95.2% level).

According to phases of treatment, the paired sample t-test clearly demonstrated the synergistic effect of nutritional support in intensive phase of treatment where rapid and maximum weight gain was observed. The mean weight gain in kilogram (kg.) with standard error (SE) was (3.43 ± 0.22) in intensive phase and (1.23 ± 0.12) in continuation phase of treatment which was mostly significant ($p < 0.001$) (Figure 2). The inadequate nutritional support was evident in continuation phase of treatment due to inadequate weight gain following recovery from disease.

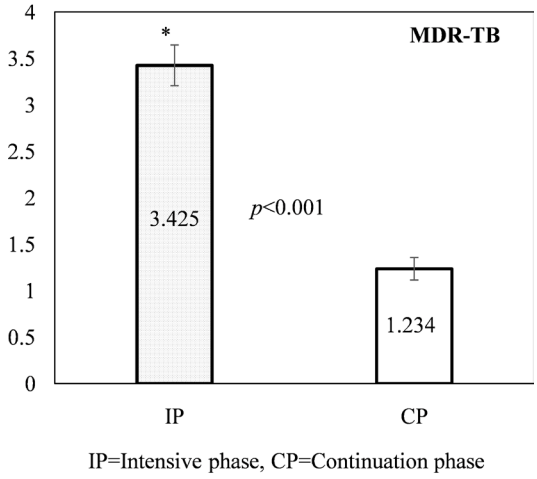

Figure 2. Mean weight gain in kilogram in different treatment phases. Mean weight gain of intensive phase (IP) and continuation Phase (CP) were expressed as Mean, where n = 187. *Significantly different from intensive phase to continuation phase of treatment at $p < 0.001$ in paired sample t-test.

4. Discussion

We evaluated the effect of nutritional support with treatment among MDR-TB patients which was expressed as weight gain over time. We also analyzed the

adequacy and access to nutritional support as adjunctive therapy in different settings. In Bangladesh, NTP is providing nutritional support only to MDR-TB patient through PMDT. On the other hand, drug susceptible TB (DS-TB) patients are still left behind. However, we found that most underweight patient's age was within 16 to 37 years (72.1%). The young age is a potential for work productivity which may cause development barrier for any country if they have malnutrition and MDR-TB. The cumulative financial losses due to disease and cost of treatment can slow down the economy of a country [24] [25]. We found that males were more prone to develop MDR-TB than females and the results of this study were consistent with previous study [25]. Several studies reported that poor treatment outcomes are predominant among MDR-TB, mostly as retreated cases and its success rate is lower than DS-TB [22] [26] [27] [28]. We also found lower treatment success rate among MDR-TB (84%) compared to national DS-TB treatment success rate (>95%) [29]. The term treatment success rate is the combination of both cured and treatment completed. The TB related technical terms such as cured, completed, failure, loss to follow up and others are properly described in WHO approved national guidelines and national PMDT guidelines [3] [5]. The unfavorable outcomes were higher among initially underweight patients (BMI < 18.5) (**Table 1**). It indicates the necessity of extra care and supports for underweight patients from the beginning of treatment. In this study, we found that MDR-TB was mostly developed among those who had poor treatment adherence during DS-TB treatment. The results of our study were validated with previous studies [25] [26] [27] [28]. Like other studies, we also observed higher deaths among MDR-TB (8.2%) than DS-TB [26] [28] [29]. However, the under-weight was more predominant (>81%) among MDR-TB (**Table 2**). This might be due to the virulence of pathogen and the rapid loss of appetite. Several studies also stated that underweight is frequent among the MDR-TB patients (68% to 75%) at baseline and they have a greater risk of deaths than normal weight [9] [26] [27]. In this study, patients received an adequate diet (three times a day) as well as financial support to purchase food as an individual's choice at hospital. Such kind of nutritional support, regular DOT and timely correction of adverse drug reaction (ADR) facilitated the rapid weight gain at CDH. The weight gain with treatment indicates the recovery from disease. However, each patient did not gain similar weight, even a few patients losses weight for a certain time; most patients ultimately gained weight after four months of treatment.

Such weight gain indicates the synergistic effect of nutritional support on treatment effectiveness (**Figure 2**). A study reported that a modest weight gain with nutritional supplementation can be a predictor of better treatment outcomes [8]. Alternatively, the possible causes of suppression of weight gain or loss of weight in some patients might be due to unidentified co-morbidity or confounders or ADR. Other studies also validated our findings that negative predictor of weight gain is associated with malignancy or co-infection with diabetes, hepatitis [6] [14]. We observed that more weight gain occurs in first two months

of treatment compared to next subsequent months. This might be due to more bactericidal effects of drugs as well as adequate and regular nutritional support at the initial stage. Subsequently, patients become stable and adjusted with treatment over time. Interestingly, male patients gained more weight in intensive phase. It may indicate higher treatment response which may due to different reproductive biology or drug tolerability that leads to less chance of unidentified co-morbidity or nutrient loss which interrupt the optimum weight gain. However, after completion of the intensive phase, despite providing monthly financial support for food with treatment at household level, under-weight did not adequately turn into normal weight; rather under-weight increased among female patients (**Table 2**). The result indicates that females were deprived to have adequate nutrition in their family. However, male patient's underweight was static, which also indicates improper food intake at the household level. Therefore, it is important to review the amount of money for nutritional support, its optimum utilization, culture and gender issues in the community. We observed that BMI progress was negatively influenced by age of patients and the trend of lower progress of BMI with increased age, particularly among males (**Table 3**). Interestingly, the tendency of lower progress of BMI was not significant among females, which may indicate different human biology, drug tolerability, and regularity in food habits and culture. Another study reported that the existing stigma hindering the treatment adherence thus may also contribute to develop MDR-TB [30]. Alternatively, adequate counseling can enhance treatment adherence [30]. Studies suggest that regular monitoring of DS-TB treatment and timely correction of ADR, advocacy to eliminate stigma, counseling and nutritional support with quality DOT would help prevent development of MDR-TB [5] [31] [32] [33] [34]. Though we expected the gradual improvement of BMI due to recovery from the disease over time, patients gained more weight in the intensive phase due to more nutrition intervention with quality DOT. Like our study, another study described that young are more physically active in their life through exposed to contact with patients and irregularity of treatment assuming to have the chance of developing MDR-TB [35]. Further study is needed to identify the other confounding factors on why and how young age groups are more vulnerable to develop MDR-TB.

5. Limitation of the study

In our study, HIV, diabetes, socio-economic condition, smoking and behavioral factors were not properly considered. The above mentioned areas may provide potential clues to the researcher for further study.

6. Conclusion

We found that nutritional support has the synergistic effect in gaining weight with recovery from disease. The more financial support to the MDR-TB patients particularly at community level would help achieve the expected gradual progress

of weight gain. High quality DOT with nutritional support to DS-TB including special focus on the malnourished group would prevent resistant, transmission, death and other unfavorable outcomes. Social and behavioral changes are also needed to address the female patients.

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Author Contributions

MAS and ZAS designed this study. MAS collected data from Hospital and different facilities in Rajshahi division. MAS, ZAS and MGH prepared and analyzed the data. TA, MMR, KH and ZAS revised this manuscript. All authors approved the final version.

Ethics and Consent

Ethical approval (No: 49/320/IAMEBBC/IBSC) for this study was taken from the Institutional Animal, Medical Ethics, Biosafety and Biosecurity Committee of Institute of Biological Sciences, University of Rajshahi, Bangladesh. Informed consent was taken from each participant.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

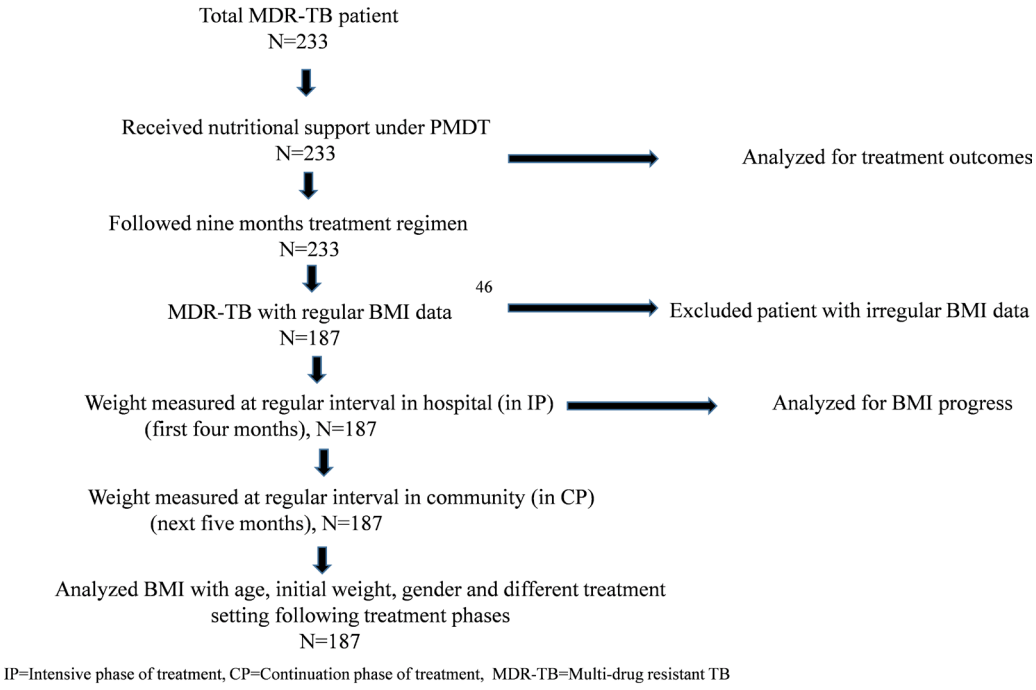

Figure S1. Diagrammatic representation of sampling protocol.