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Long-term effect of weight loss induced by bariatric surgery on asthma control and health related quality of life in asthmatic patients with severe obesity: A pilot study

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ABSTRACT

Background: The weight loss induced by bariatric surgery (BS) improves asthma clinical control evaluated usually after a short time. The long-term effects of weight loss attained by BS on asthma control and health related-quality of life (HRQoL) in patients affected by asthma and obesity are not known.
Objective: To investigate the five-year effect of weight reduction induced by BS on asthma control, quality of life and pulmonary functional parameters in severely obese intermittent or mild-to-moderate asthmatic patients.
Methods: Twenty-six consecutive severe obese subjects with previous diagnosis of asthma with indication for laparoscopic adjustable gastric banding (LAGB) were enrolled into the study. Fifteen of them agreed to undertake the surgery (treatment group, TG) while the remaining eleven non-operated patients represented the control group (CG). Body mass index (BMI), Asthma Control Test (ACT), Mini Asthma Quality of Life Questionnaire (mini-AQLQ) and spirometric parameters were evaluated at baseline and after one and five years from surgery.
Results: Mean BMI of TG significantly decreased at one and five years after the surgery, while it remained unchanged in CG. After surgery, both the overall ACT and the mini-AQLQ score significantly improved in TG after one year, persisting improved after 5-years ($p < 0.001$), while these outcomes remained unchanged in CG. As compared with the pre-surgery values, the percentage of predicted FEV_1 and FVC significantly increased at five-year follow-up from surgery in TG, while it remained unchanged in CG.
Conclusions: In severe obese asthmatic patients, the significant improvement of asthma control test and HRQoL, observed one year after LAGB, persists five years after surgery.

1. Introduction

Obesity is a global problem, with several effects on the respiratory system, predisposing to serious respiratory diseases, including asthma [1]. Several epidemiological studies have reported the association between obesity and asthma [2–4], indicating an increase in asthma severity and exacerbation [5–7], therefore burdening patient's quality of life [8] and asthma control [9,10]. Recently, the respiratory metabolic phenotype (also called "metabotype") of obese asthmatic patients has been investigated by metabolomics [11,12]. It was demonstrated that asthma associated with obesity express a respiratory metabotype that is fully different, not summatory, with respect to those separately characterizing patients with either asthma or obesity alone.

Weight loss may improve lung function, asthma control and

Abbreviations: ACT, Asthma control test; AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; CG, control group; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRQoL, health related-quality of life; LAGB, laparoscopic adjustable gastric banding; PFTs, pulmonary function test measurements; TG, treatment group.

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severity in adult obese asthmatics [13–16]. In particular, weight loss induced by bariatric surgery appears to be an effective tool to improve asthma control and symptoms, although the effect has been usually evaluated after a relatively short period [15,17–20]. Accordingly, in a one-year prospective study we demonstrated an improvement in asthma control and lung function in a group of asthmatic obese patients after weight lost induced by surgical treatment [21]. The few long-term studies (≥5 years) published so far evaluated only the percentage of asthma resolution, without considering symptoms, control or functional parameters [19,22,23]. In particular, the persistence or the reversibility of the effect induced by weight loss after long term from the bariatric surgery is not known.

In this paper, we investigated the long-term (five-year) effects of weight loss induced by bariatric surgery on asthma control and the health-related quality of life (HRQoL) and lung function in severe obese asthmatic patients.

2. Materials and methods

2.1. Patients

Twenty-six consecutive severe obese subjects with previous diagnosis of intermittent or mild-to-moderate asthma attending our bariatric surgery clinic (tertiary care) for laparoscopic adjustable gastric banding (LAGB) evaluation were enrolled into the study from April 2010 to April 2011. Fifteen of them agreed to undertake the surgery (treatment group, TG), while the remaining eleven, which refused for reasons unrelated to asthma or other health problems, represented the control group (CG).

All patients were non-smoker or had stopped smoking for two years or more. The diagnosis of asthma was made following the American Thoracic Society criteria [24]. Atopy was based on positive wheal responses (>3 mm) to 12 common airborne allergen extracts (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* and dog and cat dander), pollens (*Gramineae*, *Parietaria* species, *Betulaceae*, *Artemisia* and *Oleaceae)*, and mould *(Aspergillus, Alternaria and Cladosporium)* using a standardized skin prick test kit (Allergopharma Hamburg, Germany). Exclusion criteria included the following: cardio-respiratory disturbances, obstructive sleep apnea, and history of upper respiratory tract infection or relevant allergen exposure within 4 weeks before entering the study.

The local Ethics Committee approved the study protocol and informed written consent was obtained.

2.2. Outcomes

Six outcome parameters were considered. The Body Mass Index (BMI), the Asthma Control Test (ACT), the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) and three pulmonary functions (PFTs) (FEV_1, FVC, FEV_1/FVC).

2.3. Pulmonary function test measurements

Flow rates were determined using automated equipment (V Max 22 System SensorMedics, Milan, Italy). Forced inspiratory and expiratory maneuvers were performed three times and the best value obtained from the maximum inspiratory and expiratory flow-volume curves were used for comparison. Recommendations for standardized procedures for various lung function tests were followed [25].

2.4. Asthma control and HRQoL

To assess the asthma control and HRQoL we used the ACT and the mini-AQLQ, respectively. The ACT consists of five questions, each with a five-point scale assessing asthma symptoms (daytime and nocturnal), use of rescue medications, and the effect of asthma on daily functioning [26]. The score ranges from 5 to 25, with lower scores indicating poorer asthma control. Subjects with an ACT score <20 were defined as having not well-controlled asthma. The mini-AQLQ consists of 15 questions on symptoms, activity limitations, emotional function and environmental stimuli, each with a 7-point scale [27]. The score ranges from 1 to 7, with lower scores indicating poorer HRQoL.

2.5. Experimental procedure

The PFTs, ACT questionnaire and mini-AQLQ were performed before surgery, and repeated one and five years after the surgery in TG; at baseline and after one and five years in CG. All measurements were carried out at lunchtime. All subjects were fasted for 4 h before the tests. The subjects' weight and height were measured immediately before the start of the experiment. Patients with allergy to pollen were studied out of season. The dose and timing of long-acting β_2-agonists were identical at study visits before and after weight loss. Patients did not consume any short-acting bronchodilators for 4 h before pulmonary function tests.

2.6. Statistics

Continuous variables are expressed as mean ± standard deviation (SD) while categorical variables are expressed as rates. To evaluate the effect of the treatment at each follow-up time and the possible changes between follow-up times in each treatment group, we performed a multiple regression using as dependent variables the differences between each follow-up time and the baseline of each outcome. Being aware that the errors of the multiple (six) regression models have a great probability of being correlated, we analyzed our data by applying a “seemingly unrelated regression” model (SUR) [28] with the relative multivariate analysis of covariance (MANCOVA) (see Supplemental Data). A one-way multiple analysis of variance (MANOVA) model was used to test the differences on baseline parameters between the group of patients undergoing surgery and the control group. A one-way analysis of variance (ANOVA) on the items composing the ACT and mini-AQLQ scores changes was employed to assess whether changes observed in the global scores were attributable to one or more specific item. Data were analyzed by Stata version 13.0 (StataCorp LP, College Station, Texas). Statistical significance was accepted at $p < 0.05$.

3. Results

Baseline characteristics of patients are shown in Table 1. No significant differences were observed on baseline values of age and the six outcome variables between treatment and control groups ($p = 0.26$). Furthermore, no significant differential behavior in any of the items composing the ACT and the mini-AQLQ global score was observed between the two groups (always $p > 0.6$; Table 2).

The MANCOVA analysis shows that the main effect of the surgery (treatment) is significant ($p \leq 0.0001$) without differences between the four statistics (Wilk's lambda, Lawley-Hoteling trace, Pillai's trace and Roy's largest root). While the main effect of the follow-up time is not significant ($p = 0.088$), its interaction with the surgery is significant ($p = 0.008$). Interestingly, the model includes a significant effect of age as confounder. The lack of significance of the follow-up time ($p = 0.088$) does not imply that significant differences related to follow-up cannot be observed since the interaction term is actually significant. Therefore, specific time

Table 1
Characteristics of patients at baseline and after one and five years.

	Baseline		1 year		5 years	
	CG N = 11	TG N = 15	CG N = 11	TG N = 15	CG N = 11	TG N = 15
Sex (M/F)	0/11	3/12	0/11	3/12	0/11	3/12
Age (yr.)	34.4 ± 13.3	34.3 ± 9.4	35.5 ± 13.1	35.4 ± 9.2	39.2 ± 13.1	39.1 ± 10.2
Atopy (yes/no)	9/3	13/2	9/3	13/2	9/3	13/2
Smoking History	9 N, 2 E	14 N, 1 E	9 N, 2 E	14 N, 1 E	9 N, 2 E	14 N, 1 E
Weight (kg)	115.4 ± 11.8	119.8 ± 17.5	115.4 ± 11.8	93.1 ± 13.6	112.9 ± 11.4	79.7 ± 7.2
BMI (kg/m^2)	43.4 ± 3.7	44.2 ± 5.3	42.1 ± 2.3	34.3 ± 3.3	42.5 ± 4.0	29.4 ± 2.1
FEV1/FVC	0.75 ± 0.07	0.77 ± 0.09	0.77 ± 0.06	0.8 ± 0.08	0.76 ± 0.05	0.8 ± 0.06
FEV_1% pred	87.7 ± 13.4	83.9 ± 9.7	86.7 ± 10.7	86.1 ± 7.9	83.7 ± 8.9	88.8 ± 8.6
FVC % pred	101.9 ± 13.5	95.8 ± 6.3	98.3 ± 8.9	96.4 ± 5.9	99.0 ± 12.0	97.8 ± 8.5

BMI = body mass index; CG = obese asthmatic not operated; E = ex-smoker; F = female; FEV_1 = forced expiratory volume in 1s; FVC = forced volume capacity; M = male; N = non-smoker; TG = obese asthmatic who underwent bariatric surgery.

Table 2
Asthma control test (ACT) and mini Asthma Quality of Life Questionnaire (mini-AQLQ) in the patients at baseline and after one and five years.

	Baseline		1 year		5 years	
	CG N = 11	TG N = 15	CG N = 11	TG N = 15	CG N = 11	TG N = 15
ACT total score	**19.0 ± 2.0**	**17.8 ± 3.0**	**18.8 ± 2.0**	**21.4 ± 1.8**	**19.1 ± 1.8**	**21.8 ± 2.0**
Asthma keeps you from getting much done at work/school	4.2 ± 0.7	3.8 ± 0.7	4.1 ± 0.5	4.4 ± 0.6	4.0 ± 0.6	4.4 ± 0.6
Shortness of breath	3.2 ± 0.6	3.2 ± 0.6	3.4 ± 0.7	4.1 ± 0.6	3.5 ± 0.8	4.2 ± 0.6
Asthma symptoms wake you up	4.1 ± 0.8	3.8 ± 0.8	3.9 ± 0.7	4.2 ± 0.6	4.0 ± 0.8	4.5 ± 0.6
Use of rescue medication	3.7 ± 0.6	3.8 ± 0.9	3.7 ± 0.6	4.4 ± 0.5	3.7 ± 0.8	4.5 ± 0.5
Patient rating of control	3.8 ± 0.7	3.6 ± 0.6	3.7 ± 0.6	4.3 ± 0.6	3.9 ± 0.7	4.3 ± 0.6
MiniAQLQ score	**4.1 ± 0.7**	**4.1 ± 0.9**	**4.1 ± 0.6**	**5.4 ± 0.5**	**3.9 ± 0.6**	**5.3 ± 0.6**
Symptoms	4.1 ± 1.1	4.0 ± 1.1	4.1 ± 0.9	5.4 ± 0.9	3.9 ± 1.0	5.2 ± 1.0
Emotional	4.2 ± 0.8	4.2 ± 0.8	4.1 ± 0.8	5.4 ± 0.8	4.2 ± 0.6	5.4 ± 0.8
Environmental	4.4 ± 1.0	4.4 ± 0.9	4.5 ± 0.9	5.5 ± 0.7	4.1 ± 0.7	5.5 ± 0.7
Activity	3.5 ± 0.9	3.8 ± 1.0	3.7 ± 0.8	5.3 ± 0.6	3.4 ± 0.8	5.0 ± 0.8

CG = obese asthmatic not operated; TG = obese asthmatic who underwent bariatric surgery.

contrasts, such that reported for BMI changes, may actually reach the significant threshold. As expected, there was a significant (Breush-Pagan test $p \leq 0.001$) correlation among the residuals of the six outcome regressions, thus, the use of the SUR analysis was justified. Table 3 shows that the outcome changes with the most relevant fraction of variation explained by the independent factors is, as expected, the BMI followed by the mini-AQLQ score (75.2% and 55.6% respectively). The ACT score accounts for the 33.3% and the pulmonary function measures span from 29.1% to 46.2%. The single contrasts of interest significance between treatment levels of the changes from baseline (delta) of the six outcomes at each follow-up stage are overlaid on the plots reported in Fig. 1. Panel A shows that the changes of the mini-AQLQ index from baseline at 1 year in the treatment group are significantly greater than those observed in the control group. Moreover, this improvement remains unchanged 5 years after the surgery. Same behavior is evident in panel B from the ACT score. The expected BMI reduction one year after surgery (panel C) is significantly more prominent five years after treatment, and contrasts with the BMI stability observed in the control group. Panels from D to F report the behavior of the changes of the pulmonary function as indicated by FEV_1, FVC and FEV_1/FVC ratio. The statistically significant difference is only observed after five years of follow-up between treated and control group.

4. Discussion

The data reported indicate that in severe obese asthmatic patients, the significant improvement of asthma control score and asthma HRQoL index, observed one year after LAGB, persist five years after surgery. Of note is that the persistent BMI reduction five years after treatment is significantly lower than that observed at one year in treated patients. This reduction may trigger, at least in part, the rise of a significant treatment effect observed for functional indices five years after surgery.

To examine the long-term effect of weight reduction induced by bariatric surgery on asthma control and asthma HRQoL, we used ACT and mini-AQLQ. The questionnaires have been fully validated for use in both clinical practice and trials, and are precise measurement instruments able to detect small but clinically important changes that patients experience as a result of treatment or natural fluctuation in their asthma [26] [27].

In our study, at one year from the surgery, TG reported a significant ACT improvement in all five questions, confirming the results obtained in a different group of obese asthmatic patients [21]. As compared to CG, a higher score in mini-AQLQ for TG patients was also found after the surgery, which was apparent in the total score and in all domains. Interestingly, the improvement in both ACT and mini-AQLQ persisted five years after surgery, although no significant difference between one and five years was found. This could be explained stating that the maximum effect is reached in one year and steadily maintained through five years. On the other hand, such a stability could also be related to the criteria to evaluate the outcomes, as they may become “insensitive” and/or “aspecific” beyond a threshold, having reached a ceiling effect after one year. In general, as clearly stated: “Disease-specific quality-of-life questionnaires are designed to measure the problems that are most important to the majority of patients, but patients are heterogeneous in their experiences and priorities and no questionnaire can cover all of the problems experienced by all patients. The more that

Table 3
Seemingly unrelated Regressions (SUR) analysis.

Dependent Var.	Independent Var.	Coeff.±SE	P
Delta mini-AQLQ	Treatment	1.25 ± 0.2	≤0.0001
R^2 = 55.6%	Follow-Up Time	−0.24 ± 0.25	=0.34
	Interaction: T by FUP	6.7 ± 32.0	=0.83
	Age	0.006 ± 0.007	=0.43
	Constant Term	−0.15.5 ± 0.31	
Delta ACT	Treatment	3.7 ± 1.1	≤0.0001
R^2 = 33.3%	Follow-Up Time	0.3 ± 1.1	=0.81
	Interaction: T by FUP	−0.02 ± 1.5	=0.99
	Age	0.02 ± 0.03	=0.62
	Constant Term	−0.7 ± 0 .1.3	
Delta BMI	Treatment	−9.1 ± 1.3	≤0.0001
R^2 = 75.2%	Follow-Up Time	0.27 ± 1.5	=0.85
	Interaction: T by FUP	−4.7 ± 1.9	=0.01
	Age	0.03 ± 0.04	=0.44
	Constant Term	−2.5 ± 1.8	
Delta FEV1/FVC	Treatment	0.04 ± 0.03	=0.14
R^2 = 29.1%	Follow-Up Time	−0.06 ± 0.03	=0.07
	Interaction: T by FUP	0.07 ± 0.04	=0.07
	Age	0.001 ± 0.0009	=0.12
	Constant Term	−0.07 ± 0.04	
Delta FEV1	Treatment	0.13 ± 0.06	=0.054
R^2 = 46.2%	Follow-Up Time	−0.18 ± 0.08	=0.02
	Interaction: T by FUP	0.31 ± 0.1	=0.002
	Age	−0.002 ± 0.002	=0.51
	Constant Term	−0.03 ± 0.1	
Delta FVC	Treatment	0.15 ± 0.08	=0.07
R^2 = 41.3%	Follow-Up Time	−0.27 ± 0.09	=0.003
	Interaction: T by FUP	0.28 ± 0.12	=0.02
	Age	0.007 ± 0.003	=0.017
	Constant Term	−0.33 ± 0.11	

Mini-AQLQ = Mini Asthma Quality of Life Questionnaire; ACT = asthma control test; BMI = body mass index; FEV_1 = forced expiratory volume in 1 s; FUP = follow-up; FVC = forced volume capacity; SE = standard error; T = treatment.

the number of items in a questionnaire is reduced, the more likely it is that individual patient problems will be omitted and the instrument will lose content validity" [29].

To our knowledge, this is the first study that evaluates the long-term effect of obese asthmatic patients on asthma control, HRQoL and functional parameters. Several studies have shown a decrease in the prevalence of asthma after weight loss measured within short time from surgery (usually one year) [15,17–19]. Spivak [30] reported a reduction of drugs prescription for each co-morbidities after surgery. Dixon et al. in an uncontrolled study reported improvement in all aspects of asthma assessed, including severity, daily impact, medications needed, hospitalization, sleep and exercise clinical scores in asthmatics obese after bariatric surgery [15]. Accordingly, in a previous one-year prospective study from our group, we have shown an improvement in asthma control, especially shortness of breath and use of rescue medication, and lung function in a different group of asthmatic obese patients after weight lost induced by surgical treatment [21]. In the long-term studies performed in a population of obese patients after bariatric surgery, only the percentage of asthma resolution and the referred symptoms were evaluated, showing a resolution of this disease of 48% and 87% [19,22,23]. However, in these studies the criteria for asthma diagnosis, the functional and clinical parameters and the control and HRQoL were not reported.

In our study, we have also detected an increase in spirometric values after five years, which was present only in the TG and not in CG. These results extend the results of other studies in which the improvement in lung function, following weight reduction in obese asthmatics have been reported for one year [15,17–19]. The absence of a significant improvement of functional parameters after one year in our study might be due to the sample size dimension, together with the magnitude of the change variation (as measured by the reported standard deviations), which may, at least in part,

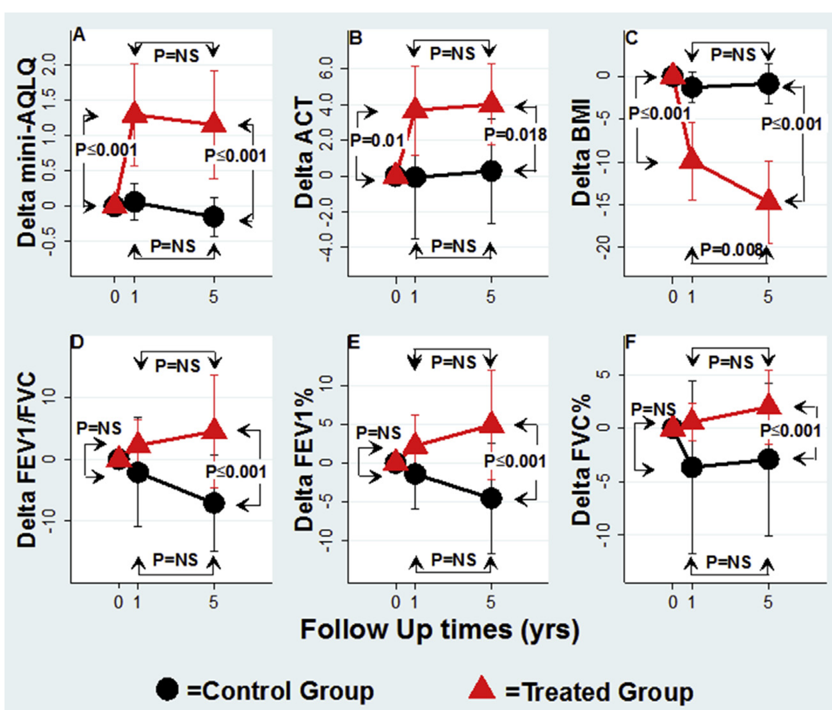

Fig. 1. Plots of changes (Delta) from baseline values of quality of life score (panel A), asthma control test (panel B), body mass index (panel C), FEV_1/FVC ratio (panel D), FEV_1 (panel E), FVC (panel F) at 1 and 5 years of follow up. Significance of the treatment effect at each follow-up and of the time effect at each treatment group are reported.
Red triangle = treated group, black circle = control group. Panel D Y axis scale is times 100. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

account for the lack of statistical power needed to get more insights in those indices.

The improvement of all outcomes we have evaluated after weight reduction may depend on several factors, including the improvement in mechanical properties of the airways, the reduction in systemic and airway inflammation and/or the reduction of co-morbidities [31]. In fact, in obese asthmatic patients early airway closure is increased during expiration and the lung periphery is more collapsed [32]. The weight reduction, which reduces closing capacity and the collapse of lung periphery, tends to improve the FEV_1 and the FVC, reducing the clinical symptoms [33]. Again, the weight reduction induced by diet [34,35] or bariatric surgery [20] may reduce airway responsiveness in obese patients with a good correlation with the reduction of BMI.

The reduction of pro-inflammatory mediators such as cytokines and several adipokines from adipose tissue induced by the weight loss may contribute the improvement of symptoms and asthma control [19,36]. Finally, the reduction of obesity-associated comorbidities due to bariatric surgery (for example, gastro-esophageal reflux disease or hypertension) should also be considered as a potential mechanism ameliorating symptoms and quality of live in obese patients [37].

The improvement observed in mini-AQLQ might also be due to an independent effect of weight loss. In fact, weight-loss interventions are usually accompanied by profound changes in physical activity and mental health, both of which may have complex independent effects on mini-AQLQ. In particular, the increased physical activity might be responsible for the improvement in both mechanical properties of lungs and asthmatic symptoms such as dyspnea. It is known that increased physical activity plays a major role in reducing dyspnea both in healthy people or in patients with respiratory disorders [38]. Thus, it is not straightforward to determine whether improvements in mini-AQLQ associated with weight loss are attributable to a reduction in body fat or, simply, to the metabolic consequences induced by increased physical activity and improved eating behavior [39].

The subjects involved in the study were consecutively recruited through the hospital's surgery department from obese patients scheduled for bariatric surgery, therefore excluding patients with severe asthma and/or severe comorbidities and complying with the strict surgical protocol. However, some limitations apply to our study. First, treatment allocation was not randomized; thus, even if patients in the control group share with treated subjects equal surgery indications, overlapping clinical and functional profile and do not show significant differences on baseline parameters, a possible selection bias cannot be excluded. Second, we did not evaluate the molecular aspects of weight loss on airway hyperreactivity or inflammatory status, which could have shed light on the improvement in spirometric function and asthma symptoms and control, therefore clarifying the issue of mechanical properties of the airways and/or the inflammation reduction. Third, the sample size of the study population was limited, but because of the surgical protocol. However, the magnitude of the observed differences between TG and CG allowed a statistically significant detection. Finally, we have evaluated the obesity only by BMI, which does not truly reflect the real individuals' fat or lean mass [37].

In conclusion, we think that the "durable" asthma control and HRQoL associated to the persistent weight reduction induced by laparoscopic adjustable gastric banding may represent an important benefit for severe asthmatic patients.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2017.06.010.

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