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Normocaloric Diet Improves Asthma-Related Quality of Life in Obese Pubertal Adolescents

Jorge Agustin Luna-Pech[a, f] Blanca Miriam Torres-Mendoza[b, d]
Jose Antonio Luna-Pech[e] Cecilia Yvonne Garcia-Cobas[a]
Susana Navarrete-Navarro[c] Alejandro Manuel Elizalde-Lozano[g]

[a]Allergy Service, UMAE Hospital de Especialidades, [b]Centro de Investigación Biomédica de Occidente (CIBO) and [c]UMAE Hospital de Pediatría, Instituto Mexicano del Seguro Social (IMSS), [d]Departamento de Clínicas Médicas, Centro Universitario de Ciencias de la Salud, University of Guadalajara, and [e]Department of Nutrition, University of the Valley of Atemajac (UNIVA), Guadalajara, and [f]Faculty of Medicine and [g]University Center for Biomedical Research, University of Colima, Colima, Mexico

Key Words
Asthma · Obesity · Diet · Quality of life · Adolescents

Abstract
Background: Restrictive, very low-energy diets focused on rapid weight loss have proven to be effective in improving asthma outcome in obese patients, but their use in children and pubescents is controversial due its potential consequences in growth. More conservative, normocaloric schemes are suggested as a more suitable dietary approach for these patients. ***Methods:*** A randomized clinical trial was run of 51 pubertal adolescents with asthma and obesity, who were allocated to either an interventional 28-week program of normocaloric diet based on normal requirements for height and meal planning (n = 26) or a non-interventional (free diet) control group (n = 25). Asthma-related quality of life (AR-QOL, assessed by the Standardized Pediatric Asthma Quality of Life Questionnaire, PAQLQ[S]) and clinical indicators of asthma control were measured before and after the intervention period. ***Results:*** Diet intervention was associated with a significant improvement in AR-QOL in relation to baseline (Δ PAQLQ[S] scores) compared with controls, both in overall score ($p < 0.001$) and its subdomains (activity limitation, $p < 0.001$; symptoms, $p < 0.002$; emotional function, $p < 0.001$). The group with normocaloric diet observed a significant decrease in body mass index z-score, which correlated positively with the improvement in AR-QOL (Spearman's $r = 0.51$, $p < 0.01$), in addition to have significantly fewer events of acute attacks of asthma and nighttime awakenings, plus a non-significant reduction in the use of inhaled corticosteroids. No significant changes were observed in the pulmonary function tests. ***Conclusion:*** The normocaloric dietary intervention was associated with improvement of AR-QOL and some aspects of asthma control. Such structured dietary programs could probably have a role as a complementary non-pharmacological therapeutic strategy in obese pubertal adolescents with asthma.

Introduction

Asthma and obesity are chronic clinical entities highly prevalent in adolescents [1]. It is now well recognized that asthma and obesity share some aspects in their pathophysiology, and that elevated body mass index (BMI) is associ-

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Correspondence to: Dr. Jorge Agustín Luna-Pech
Allergy Service, UMAE Hospital de Especialidades
Instituto Mexicano del Seguro Social Belisario Domínguez 1000, Colonia Independencia
44349 Guadalajara, Jalisco (Mexico)
E-Mail lunapech@hotmail.com

ated with the dose-dependent increase in asthma incidence and severity, particularly in the young Hispanic population [2–4]. The main international guidelines for the management of asthma recognize the impact of obesity on asthma from the clinical and pathophysiological perspectives [5, 6]. However, these guidelines do not yet consider or recommend specific dietary strategies regarding diet constituents that should be consumed or avoided to affect asthma.

Some controlled studies have found that the use of very low-energy diet programs focused on rapid loss of weight in obese people is associated with improvement of various aspects of asthma control, including pulmonary function tests, symptom scores and less frequent use of medication [7–9]. Although such programs seemed to be effective in adults and postpubertal adolescents, the benefit of a hypocaloric, highly restrictive diet regimen in the nutritional management of obesity in pubescents constitutes a controversial issue, considering its potential adverse effects in patients who have not completed their pubertal growth spurt, and in whom metabolic programming includes gradual increases of weight and height [10, 11]. According to a review from the Cochrane group studying nutritional interventions in asthma [12], the expected role of highly restricted dietary interventions is not yet clearly established and, therefore, cannot currently be recommended as part of the routine therapeutic approach for these patients. In pubertal adolescents who are obese, a more conservative, macronutrient-balanced, normocaloric diet (ND) regimen focused on weight maintenance has been proposed as a more adequate dietary strategy [13, 14].

Our main objective was to evaluate whether a program of supervised ND would improve asthma-related quality of life (AR-QOL), specifically in obese pubertal adolescents with asthma. Secondarily, we assessed the effects of the dietary program on some clinical indicators of asthma control.

Materials and Methods

Patients

Adolescents (aged 12–16 years) were recruited in the Allergy Service of a tertiary referral hospital in Guadalajara, Mexico (UMAE Hospital de Pediatría, IMSS), where they were invited to participate in the study if they fulfilled the following criteria: (1) asthma, established according the diagnostic criteria of the Global Initiative for Asthma (GINA) [5]; (2) in a stable phase of the disease (no recent exacerbation – within 15 days – or change in the antiasthmatic medication scheme prescribed); (3) obesity (BMI ≥95th percentile of the CDC BMI-for-age growth charts) [15]; (4) in the pubertal stage of the Tanner scale (stage 2–3) for both sexes [16]; (5) skin prick testing for allergy positive for at least one allergen (*Alternaria alternata*, cockroach mix, dust mite mix, cat, dog, tree mix, grass mix), and (6) forced expiratory volume in 1 s (FEV_1) >80% from the predicted value for age and height according to the American Thoracic Society guidelines [17]. All adolescents were medically treated for asthma following the stepwise approach suggested by GINA for at least 6 months. No patient was allowed to participate in the study if he/she was partaking in another prescribed dietary program, undergoing allergen immunotherapy or had other chronic diseases or comorbidities. The trial was registered and approved by the Health Research and Ethics Committee of the hospital (R-2010-1302-23), and written informed consent was obtained from both the patients and their parents.

Study Design

Prior to the beginning of the study, the patients were submitted to a 2-week run-in period that consisted of filling in a written dietary and respiratory symptoms recall in order to corroborate the stability of asthma and the adherence to the researcher's instructions. At the end of the run-in period, they were randomly allocated to either a program of supervised ND or a control group with no intervention in feeding or eating habits (free diet, FD, group). Both groups were given instructions to fill in a daily 24-hour dietary recall at home, and were programmed to attend follow-up visits every 2 weeks for a total period of 28 weeks. Follow-up visits consisted of interaction with the patients in sessions of 45 min, regardless of group allocation, (1) to assess some aspects of asthma control (i.e. need of rescue and basal medications – particularly inhaled corticosteroids – nighttime awakenings and frequency of acute asthma attacks), (2) to review the dietary recall, (3) to perform peak expiratory flow (using a Mini Wright peak flow meter) and (4) to establish an action plan in case of a worsening of asthma symptoms. Also, at each follow-up visit BMI (kg/m^2) was calculated based on weight and height measured by a digital scale (Tanita WBG-800) and stadiometer, respectively, and then converted to BMI z-scores [15]. In the corresponding group, the follow-up visits also served to assess the ND program.

At baseline and final visits the patients were asked to respond to the Spanish version of the Standardized Pediatric Asthma Quality of Life Questionnaire (PAQLQ[S]) [18], a validated instrument suitable for ages 7–17 years that evaluates overall AR-QOL through its different subdomains (symptoms, activity limitation and emotional function), rated on a 7-point interval scale (from 1 = severe impairment to 7 = no impairment). Ordinary scheduled medical follow-up was assigned to a single pediatric allergist, who was blinded to group allocation.

Program of ND

The diet program was adjusted at follow-up visits by a certified nutritionist according to the individual feeding habits and preferences of the patients by recommending variations in the menus based on an equivalent exchange system using food lists with a group of measured or weighted foods of approximately the same nutritional value, and explaining that each item on a list may be interchanged in an equivalent measured portion with a choice of any other food item on the same list, in order to provide adequate macronutrient proportions. Individual energy needs were calculated according to the resting energy expenditure recommended by the guidelines of the FAO/WHO (adjusted by age and gender), applying mild or moderate physical activity criteria and individually adjusted to length [19]. The suggested distribution of caloric

Table 1. Demographic and clinical characteristics of the enrolled children at baseline

	ND group (n = 26)	FD group (n = 25)
Anthropometric and sociodemographic variables		
Age, years	14±0.7	14±0.3
Gender		
Male	12 (46.2%)	14 (56%)
Female	14 (53.8%)	11 (44%)
Weight, kg	57.9±8.0	53.8±7.1
Height, m	1.44±0.9	1.38±0.8
BMI, kg/m^2	28.3±0.9	27.1±0.9
BMI z-score	2.18±0.3	2.17±0.2
Pulmonary function		
FEV_1, l	2.74±0.5	2.15±0.4
FEV_1 (% of predicted)	92 (12.9)	91 (15.8)
FVC (% of predicted)	94.8 (7.6)	90.4 (7.2)
FEV_1/FVC	0.87±0.2	0.85±0.2
AR-QOL (PAQLQ[S] score)		
Overall (total) score	3.4 (1.6)	3.5 (1.1)
Activity limitation	3.6 (1.4)	3.8 (1.7)
Symptoms	3.7 (1.4)	3.8 (1.7)
Emotional function	3.7 (1.2)	4.0 (1.4)
Accumulated dose of inhaled budesonide, μg/day	532±218	542±266

Continuous data are presented as means ± SD, nominal data as frequencies (with percentages in parentheses) and ordinal data as medians (with interquartile ranges in parentheses). In all variables $p > 0.05$ (Mann-Whitney U test for continuous data, χ^2 test for categorical and ordinal data).

Table 2. Distribution of intake of macronutrients after the 28-week period, by group of study

	ND (n = 26)	FD (n = 25)	p
Energy, kcal/day	2,231±231	3,243±278	0.001
Carbohydrates			
% of total caloric intake	51 (11)	68 (32)	
g/day	72±18	161±70	0.001
Fat			
% of total caloric intake	30 (3)	42 (15)	
g/day	31±9	65±10	0.01
Saturated fat			
% of total caloric intake	7 (2)	18 (6)	
g/day	9±4	23±10	0.02
Protein			
% of caloric intake	15 (4)	10 (3)	
g/day	32±9	23±12	0.09 (NS)

Continuous data are presented as means ± SD and ordinal data as medians (with interquartile ranges in parentheses). Mann-Whitney U test was used for p values. Source: written dietary recalls. NS = Non-significant.

intake was as follows: 10–15% proteins (preferably high biological value proteins, i.e. fish, lean meat, egg white), 50–60% carbohydrates (limiting consumption of simple or refined carbohydrates to <10% of the total caloric intake, and suggesting to use non-nutritive sweeteners, i.e. saccharin, aspartame, sucralose and acesulfame K), and 25–30% fat (<10% saturated fat, up to 10% monounsaturated fatty acids, and the remaining in the form of polyunsaturated fatty acids), with a daily meal pattern of breakfast (25% of daily caloric intake), lunch (30%), snack (15–20%) and dinner (25–30%). In addition, patients were encouraged to freely consume simple water if thirsty.

Calculations of the caloric and macronutrient intake obtained from the dietary recalls were analyzed through the Nutrient Data System for Research software, version 4.01, developed by the Nutrition Coordinating Center of the University of Minnesota [20].

Statistical Analysis

The sample size was calculated with the aim of detecting the minimum change in PAQLQ(S) score established as clinically important according to the developers of the questionnaire ($\Delta \geq 0.5$) [21], with a power of 80%. The Wilcoxon signed-rank test was used for intragroup comparisons, whereas the between-group differences were analyzed by the Mann-Whitney U test. Spearman's rank correlation coefficient determined the level of association between anthropometric and AR-QOL variables. Asthma control outcomes were contrasted by Fisher's exact test. All tests were 2-tailed; p values ≤0.05 were considered significant.

Results

Patients

A total of 58 adolescents aged 12–16 years (mean age 14 years; 28 male) were enrolled, of whom 29 were allocated to the active ND group and the remaining to the FD group. Both groups were well matched for demographic and clinical characteristics (table 1); 6 patients (2 from active diet program and 4 controls) dropped out during the first 9 weeks, 1 adolescent from the control group withdrew by moving out of the area, and 3 (as well as 2 from the ND group) were lost to follow-up. At baseline, adolescents assigned to ND presented non-significant higher absolute FEV_1 values than their control counterparts; however, there were no differences in percent predicted, as patients with ND tended to be heavier and taller than those in the FD group (p = 0.18 and 0.10, respectively). Overall, 51 patients (88% of the enrolled) completed the study.

Anthropometric Assessments and Adherence to the Dietary Program

Calculation of energy and macronutrient intake showed a significant and sustained decline in the active group, contrary to controls (table 2), which constitutes an indirect inference to the level of accomplishment and adherence

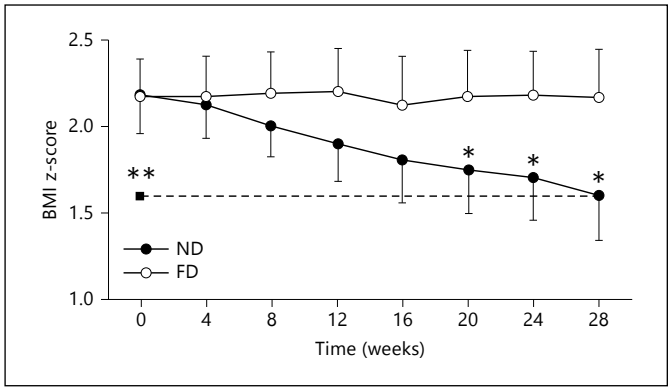

Fig. 1. Time trend of the BMI z-score at 4-week cutoff points throughout the 28-week period. At the end of the study, the mean (± SD) BMI z-score in the ND group showed a significant decline both in the paired intragroup comparison vs. baseline ($p = 0.02$) and the between-group comparison with FD controls beginning at week 20 ($p = 0.04$ at 20 weeks, $p = 0.03$ at 24 weeks and $p = 0.01$ at 28 weeks). The closed square superposed to the first visit column indicates the comparison point between the basal and final BMI z-score in the active group. * $p < 0.05$ (Mann-Whitney U test); ** $p < 0.05$ (Wilcoxon's signed-rank test).

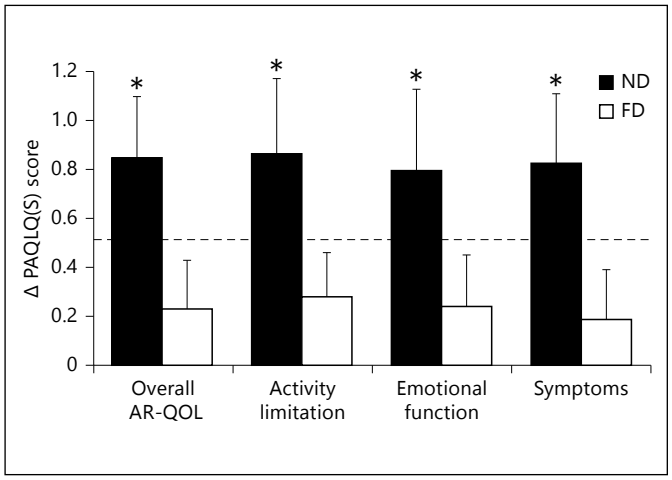

Fig. 2. Adolescents who underwent the ND program (n = 26) had significantly greater improvements in AR-QOL (higher PAQLQ[S] scores) compared with controls (n = 25). The dotted line indicates the cutoff point of the criteria of minimally significant difference change score ($\Delta = 0.5$). Data are presented as means ± SD. * $p < 0.05$ (Mann-Whitney U test).

to the dietary program. As shown in figure 1, at the end of the follow-up period the mean BMI z-score remained practically unchanged in the FD group, in contrast with the ND group in which a significant decline in the mean BMI z-score was demonstrated both when compared with baseline (2.18 ± 0.3 vs. 1.66 ± 0.2, $p = 0.02$; Wilcoxon's test) and in the between-group comparison with controls (1.66 ± 0.2 and 2.12 ± 0.3 respectively, $p < 0.01$; Mann-Whitney U test), as well as the between-group pre/post value of weight (–2.5 ± 1.3 kg in the ND group vs. 1.6 ± 1.3 kg in the FD group, $p < 0.03$). The nutritional status at the end of the intervention period also presented changes in the active diet group, as 15 patients (57%) achieved conversion from obese to overweight (BMI-for-age centiles between 85 and 95%). Conversely, all 25 adolescents with FD remained under the criteria for central obesity at the end of the study. Also, there were no significant differences between the anthropometric responses in the stratified subanalysis by gender of either of the groups.

AR-QOL and Asthma Control

The dietary intervention was related to a significant improvement in AR-QOL (PAQLQ[S] scores) compared with controls, and this difference was achieved both in the overall score ($p < 0.001$) and all its subdomains (symptoms: $p < 0.002$, activity limitation: $p < 0.001$ and emotional function: $p < 0.001$), as depicted in figure 2. In addition, the improvement of overall AR-QOL in adolescents under the dietary program, but not in controls, correlated positively with the aforementioned reduction in mean BMI z-scores (fig. 3). The active diet group reported significantly fewer acute asthma events requiring rescue medications (i.e. short-acting β-agonists) at the end of the study compared with controls (17 vs. 39, respectively, $p < 0.02$), as well as nighttime awakenings (11 vs. 26, $p < 0.001$). The daily dose of inhaled corticosteroid reduced at a rate of ≥100 μg/day of aerosolized budesonide (the inhaled corticosteroid with higher prevalence of use in our hospital) in 11/26 (46%) of the adolescents with ND, in contrast with 6/25 (24%) in the FD group, albeit this difference was not significant (table 3). Finally, in cross-sectional data analysis at the end of the study, only marginal increases in absolute FEV_1 values were found, more evidently (but non-significant) in those with ND; no correlation was found between the overall PAQLQ(S) Δ score and FEV_1, forced vital capacity (FVC) nor FEV_1/FVC, independently of group allocation (data not shown).

Discussion

There are still relatively few controlled and methodologically competent studies concerning the benefits of a dietary intervention in AR-QOL in pediatric obese pa-

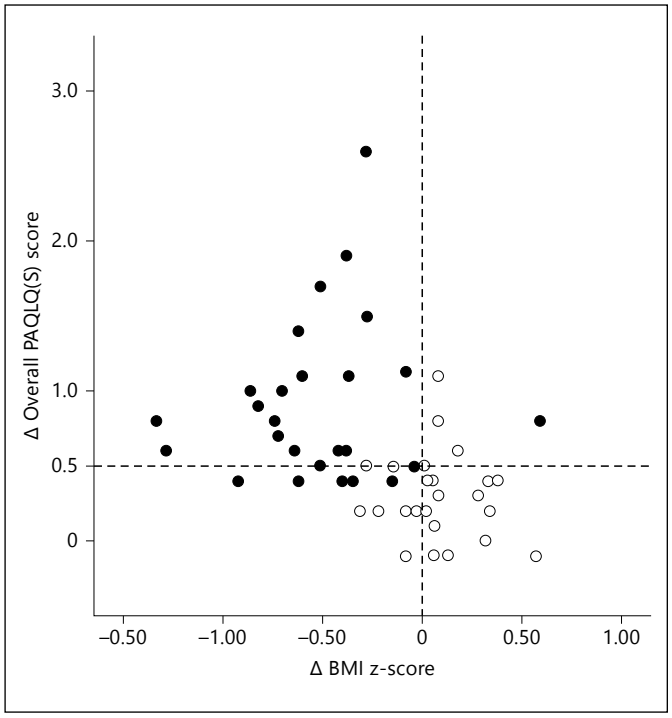

Fig. 3. Relationship between changes in overall AR-QOL (Δ total PAQLQ[S] score) and Δ BMI z-scores in adolescents with ND (closed circles, n = 26) and FD (open circles, n = 25) after the 28-week period. Note that Δ BMI z-score correlated positively with the improvement in overall AR-QOL (r = 0.51, p = 0.01, Spearman's test) in the intervention group, but not in controls (r = –0.02, p = 0.8). Reference lines indicate the cutoff point of the criteria of minimally significant difference change score (Δ PAQLQ[S] = 0.5) and baseline of BMI z-score.

Table 3. Changes in the daily doses of inhaled budesonide at the end of the 28-week trial (supervised dietary program with ND vs. FD)

Group	ND (n = 26)	FD (n = 25)	Total
Decrease (<100 μg/day)	12 (46%)	6 (24%)	18
Unchanged	12 (46%)	14 (56%)	26
Increase (>100 μg/day)	2 (8%)	5 (20%)	7

p = 0.09 (Fisher's exact test).

tients [8, 9, 22], and most of the previous trials have included pubescents together with adults or younger children, which could induce some bias considering the particularities in terms of growth rate of this particular age group. da Silva et al. [23] documented the positive effects of a low-energy diet in obese asthmatic adolescents, but they focused their study on postpubertal patients only (Tanner stage 5), on whom more restrictive diet regimens could be recommended. To the best of our knowledge, our study constitutes the first effort intended to report the effects of a dietary intervention on AR-QOL and disease control in obese pubertal adolescents exclusively.

Weight loss is a useful therapeutic strategy for those obese patients who suffer from chronic pulmonary disease. In spite of the fact that ketogenic-becoming or highly restrictive dietary regimens can lead to a reduction in corporal mass in a shorter period of time, these regimens are contraindicated in early adolescence except in selected very severe cases, as they can alter the natural expected weight gain that depends on new lean muscle mass that is a particularity of this age period and thus potentially affect the growth [10, 24]. Our decision to use a more cautious and prolonged program of supervised ND with careful balance in macronutrients was founded on the fact that there is enough body of evidence to show that such a nutritional strategy favors 'grow into their weight', induces losing weight more gradually (which could be related to a more sustained clinical effect), is associated with less rebound effect, facilitates fitness, and ultimately can help to improve some psychosocial variables without affecting growth [13, 14, 25].

Patients in the ND program demonstrated significant improvement in the overall PAQLQ(S) score and its 3 subdomains. To better establish clinical relevance, we calculated the number-needed-to-treat to be 1.7 (95% CI = 1.2–2.6), being the number of adolescents that would need to be treated with diet for 1 to have a clinically meaningful improvement in their AR-QOL compared with FD. Also, the overall reduction in BMI z-score in the active diet group correlated positively with the improved perception of AR-QOL at the end of the study. Interestingly, some adolescents in the control group also showed improvement in AR-QOL, but without reaching significant changes with respect to baseline to be considered clinically important (Δ ≥0.5). This could probably be explained by the fact that all patients were programmed to asthma education visits more frequently than their ordinary medical schedule. In these terms, as has been established in a number of studies [26, 27], it is possible that certain psychosocial elements, like better adherence to treatment as a consequence of better acknowledgment of their disease, in addition to gradual changes in confidence and self-care, could have been related to the modest improvement in AR-QOL achieved by the FD group, despite remaining obese.

Data from recent systematic reviews [9, 28] have consistently suggested that some interventions based on weight loss in obese asthmatics could be associated with an improvement in asthma control. Our results are consistent with this suggestion, with an overall improvement compared with baseline in some clinical aspects of asthma control in the ND group (particularly less frequency of nighttime awakenings and acute episodes of asthma that required rescue medications), albeit some differences were not significant when compared with controls (as was the case in the need for inhaled corticosteroids and the improvement in the personal best peak expiratory flow). We can assume that this study could not have the adequate power to demonstrate a more prolonged effect of diet with respect to the use of inhaled corticosteroids and rescue medications. Therefore, further studies should be undertaken in order to conclude that an improvement in asthma control could, at least partially, be related to the nutritional intervention. Additionally, we observed only slight changes in FEV_1 and FVC, regardless of the significant reduction of weight and BMI z-score in the active diet group. These findings, in contrast with results from other similar studies [8, 9], are explained in part by the fact that the basal measurements of our patients were already normal, as stable asthma (FEV_1 >80% predicted) was one of our inclusion criteria. We also speculate that this mild improvement in pulmonary function in the ND group could also be compatible with the current concept that changes in lean mass, not fat mass, show much better association with lung function in children with asthma [29].

At the end of the follow-up, both the mean weight and the BMI z-score showed a significant decline in the patients with ND in contrast with controls, in whom these two indicators even showed modest increases. It is important to emphasize, though, that the most representative effects observed in our intervention in terms of BMI reduction were observed after the tenth week of the study, reaching statistical significance only after the twentieth week. This finding is consistent with the aforementioned potential effects of the ND regimen in adolescents, in which it was expected that an early phase of weight maintenance followed by a gradual decline of weight as the growth rate progressively reaches a balance between weight and height. We also hypothesize that this early non-response period could have been related to the lack of a concomitant exercise program, which, complemented by the dietary program, could have probably favored a more rapid and sustained beneficial effect. Nevertheless, we decided not to prescribe additional interventions beyond the pharmacological asthma treatment in order not to downplay the role of diet as a complementary treatment.

A very interesting study by Gold et al. [30] has stated that obesity effects in terms of risk of development of asthma could be greater in pubertal females, as the age of peak lung growth occurs earlier in women than in their male counterparts, so the effects of the dietary program regarding gender differences are of more importance. However, in the stratified subanalysis by gender we did not find significant differences in the outcome of AR-QOL, pulmonary function tests or the level of control of the disease, both in the between-group and intragroup comparisons at the end of the study. We speculate that the effect of gender in the development of asthma in our patients could have been attenuated by focusing on adolescents with pre-established obesity and stable asthma, as more effects of obesity in women have been noted more specifically in subjects with rapid weight gain in a period of 1 year [30].

This study has some limitations. QOL questionnaires are prone to high variability and low precision in fully translating the real perception of the individual concerning their medical condition, whence it is possible to fall into information bias at the moment of the fulfillment of the survey. Adherence to the dietary program was measured by a dietary recall, which could be subject to manipulation (essentially omissions). Due the nature of the intervention, the study could not be blinded, and this could have induced investigator bias. Furthermore, receiving an active intervention versus receiving no intervention could have generated placebo bias, especially when the end point is subjective. This could be further relevant in this age group, who are psychologically sensitive to weight gain, as has been recently discussed by Brashier and Salvi [31]. Lastly, the probable physiopathogenic mechanisms implied in the observed effect of the dietary intervention could have been better assessed by measuring some biochemical markers appropriate to the minimal inflammatory state associated with obesity (i.e. cytokines, leptin, adiponectin), as well as the measurement of complementary biomedical indicators more focused on body composition rather than BMI alone, such as visceral fat thickness and bone mineral density, plus the additional potential effect of other interventions.

In summary, a 28-week program of supervised and macronutrient-balanced ND is effective in gradually improving AR-QOL in obese pubertal adolescents, and, secondarily, could be related to positive consequences in terms of asthma control. Structured dietary programs

could have a role as a complementary non-pharmacological therapeutic strategy for the treatment of this kind of patient. Further larger studies are needed in order to establish the full efficacy of this nutritional intervention and to better define the specific mechanisms involved in its effects.

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