Antioxidant supplementation and exhaled nitric oxide in children with asthma

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ABSTRACT

Background: *The effect of allergen avoidance on airway inflammation is similar to that observed with treatment with inhaled steroids, whereas inhaled steroids have no effect on oxidative stress–induced inflammation.*

Objective: *The aim of this study was to retrospectively evaluate the potential effect of an antioxidant dietary supplement on exhaled nitric oxide over a month in pediatric patients on stable antiasthma treatment.*

Methods: *Forty-seven children with moderate-to-severe asthma were retrospectively evaluated.*

All the patients were sensitive to Dermatophagoides pteronyssinus and Dermatophagoides farinae, and they were receiving the minimum inhaled corticosteroid dosage required to maintain adequate control. Within a few weeks of admission at Misurina Hospital in the Alps, the regular treatment was gradually reduced, then some children who were receiving a daily dose of inhaled corticosteroids, ≤200 mcg of fluticasone propionate, were prescribed a nutraceutical dietary supplement for at least 4 weeks. Lung function and fractional exhaled nitric oxide (FeNO) measurements were recorded at the beginning and after 1 month of the dietary supplementation.

Results: *Baseline lung function and FeNO values did not differ between the two groups of patients. After 4 weeks of nutraceutical supplementation, FeNO values decreased, from 19.00 ppb (interquartile range, 14–31 ppb) to 11.00 ppb (interquartile range, 6–23 ppb) ($p = 0.03$). No significant reduction was observed in the group that did not receive the supplementation, and no significant difference between groups was observed, both at baseline and after 4 weeks of nutraceutical supplementation.*

Conclusion: *Supplementation with a nutraceutical of antioxidants and anti-inflammatory compounds, such as curcumin, resveratrol, soy phospholipids, zinc, selenium, and vitamin D, may be associated with reduced airway inflammation, as documented by a fall in FeNO.*

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Allergen avoidance in children with asthma who were admitted to a residential house (Istituto Pio XII) located at high altitude (1756 m above sea level) in the Italian Alps was shown to be associated with a reduction of several inflammatory parameters, such as basophil histamine release,[1] sputum eosinophils, exhaled breath condensate cysteinyl leukotrienes, leukotriene B4, and 8-iso-prostaglandin F2α.[2] In particular, exhaled nitric oxide was observed to significantly decrease within 2 weeks of staying in the residential house.[3] Thereafter, the level of exhaled nitric oxide reaches a plateau, with no further reduction, even if children remain in the mite-free environment.[4]

Oxidative stress plays an important role in the immune response to foreign pathogens and allergens in the airways, and has a significant role in exacerbation of asthma as it is related to the release of reactive oxygen species from neutrophils or respiratory tract epithelial cells.[5] A number of studies underline the role of oxidative stress in human disease and indicate the protection against reactive oxygen species by means of antioxidant compounds.[6] The effect of allergen avoidance on airway inflammation is similar to that observed with treatment with inhaled steroids,[7] whereas inhaled steroids have no effect on oxidative stress–induced inflammation.[8] For this reason, the aim of the study was to retrospectively evaluate the potential additive effect of an antioxidant dietary supplementation, which has been demonstrated to be sensitive in detecting oxidative and/or nitrosative stress in asthmatic airways, on exhaled nitric oxide[9] during a period of stay in a mite-free mountain environment in children on stable antiasthma treatment.

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Envicon Medical Srl supplied the dietary supplement for this study

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METHODS

Patients

Forty-seven children with moderate-to-severe asthma according to the definition of the American Thoracic Society[10] (mean [standard deviation] age, 12.1 ± 3.1

Table 1 **Data for demographics and treatment**

	Total	Supplemented Group	Not Supplemented Group	*p* Value
No. subjects	47	15	32	—
Age, mean (SD), y	12.1 ± 3.1	11.1 ± 3.3	12.6 ± 3.0	—
Boys, no. (%)	30 (63.8)	11 (73.3)	19 (59.4)	—
Weight, mean (SD), kg	48.6 ± 16.5	45.0 ± 13.9	50.3 ± 17.6	0.29
Height, mean (SD), m	152.6 ± 16.9	150.0 ± 18.7	153.8 ± 16.2	0.55
BMI, mean (SD), kg/m^2	20.2 ± 3.7	19.5 ± 3.1	20.5 ± 4.0	0.39

SD = standard deviation; BMI = body mass index.

years) were retrospectively evaluated. All the patients were sensitive to house-dust mites (HDM), *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, as demonstrated by positive skin-prick test results for the allergens, and they were receiving the minimum inhaled corticosteroid (ICS) dosage required to maintain adequate control.[11]

All the children were guests for at least 3 months at the Instituto Pio XII in Misurina in the Italian Dolomites (1756 m above sea level), where routine analysis for HDM always failed to reveal the presence of mite allergens. The patients' characteristics at the time of the study are reported in Table 1.

Study Design

At the time of admission to the residential house, the children were on regular treatment with ICS plus a second or a third controller medication (either salmeterol or montelukast, or both). Within a few weeks of admission, the regular treatment was gradually reduced because of symptom improvement, and the patients were maintained either on a low dose of ICS or without any regular treatment. After at least a 1-month stay, a nutraceutical dietary supplement that contained curcuma longa with soy phosphatidylcholine (Meriva; Indena SpA, Milano, Italy) (100 mg), resveratrol (20 mg), folic acid (90 mcg), soy isoflavones (15 mg), magnesium (300 mg), zinc (7 mg), selenium (55 mcg), and vitamin D (15 mcg) (Auxilie Immuplus; Envicon Medical Srl, Verona, Italy), kindly supplied by Envicon Medical Srl, was administered for at least 4 weeks to a group of children who were receiving a daily dose of ICS, ≤200 mcg of fluticasone propionate. The administration of the nutraceutical dietary supplement was based on the personal choice of one of the physicians (L. Z.) who operate in the residential house to include such a supplementation in the children while under her care, based on the suggested effect of antioxidant supplementation in allergic disease.[12] This group was retrospectively compared with a similar group of children guests of the residential house Pio XII followed by other physicians who did not supplement children with antioxidant nutraceuticals.

Lung function and fractional exhaled nitric oxide (FeNO) measurements were recorded regularly for all the children who were staying at the residential house, and, for the purpose of this report, the values recorded at the beginning and after 1 month of the dietary supplementation with the nutraceutical compound were taken into consideration. Favorable ethical permission to analyze the data for our study purposes was obtained from the Ethics Committee for Clinical Trials Treviso-Belluno Ethics Committee (Title: Antioxidant in childhood asthma [*Antiossidanti in asma infantile*]).

Spirometry and FeNO Measurements

Spirometry was performed by an electronic spirometer (Master Screen IOS; Jaeger, Hoecheberg, Germany), calibrated before the arrival of each subject by using a 3-L syringe (Jaeger). The forced vital capacity maneuvers were carried out with the child standing and while using a nose clip. The subjects were instructed to avoid the use of short-acting bronchodilators for at least 6 hours before undergoing testing. The tests were always performed at the same time of day.

Exhaled nitric oxide was measured by using a portable HypAir FeNO machine (Mèdisoft, P.A.E de Sorinne, Sorinne, Belgium). Briefly, the children were asked to exhale slowly a single time through a mouthpiece against a resistance. A biofeedback device maintained a 5–6 L/min steady expiratory flow, which assured the closure of the soft palate and separated the nasopharynx from the oropharynx. FeNO values were registered at the plateau of the end-exhaled reading according to the guidelines.[13] FeNO measurements were always performed before spirometry.

Statistical Analysis

The *p* values of <0.05 were considered statistically significant. All calculations were done by using GraphPad Prism (GraphPad Software, Inc., La Jolla, CA) for Windows. Data were compared by nonparametric sample tests *viz.* the Mann-Whitney unpaired test and Wilcoxon paired test, as appropriate.

Table 2 **Lung function and FeNO values (median [interquartile range])**

	Supplemented Group			Not Supplemented Group		
	T0	T1	*p* Value	T0	T1	*p* Value
FVC*	97.6 (90.4–111.4)	104.6 (95.0–110.2)	0.63	107.4 (94.0–112.6)	106.8 (95.4–114.5)	0.80
FEV_1*	99.6 (90.7–111.1)	110.0 (95.1–119.1)	0.29	110.1 (98.6–122.0)	112.6 (95.5–120.1)	0.81
FEV_1:FVC*	103.0 (88.0–113.5)	103.3 (94.0–115.8)	0.55	101.7 (93.9–109.3)	104.1 (96.5–110.2)	0.81
FEF 25–75*	86.0 (58.4–126.0)	102.7 (68.4–120.8)	0.56	94.1 (77.5–118.2)	99.5 (82.8–126.3)	0.73
ΔFEV_1#	4.5 (−2.3 to 21.4)	2.0 (−0.9 to 9.1)	0.59	4.15 (−0.2 to 8.9)	4.8 (1.7–8.7)	0.58
FeNO	19.0 (14.0–31.0)	11.0 (6.0–23.0)	0.03	18.0 (10.5–26.5)	16.0 (9.5–22.5)	0.13

FeNO = fractional exhaled nitric oxide; T0 = baseline; T1 = after 4 weeks of nutraceutical supplementation; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; FEF 25–75 = forced expiratory flow at 25–75%.
**Percentage of predicted value.*
#Reversibility after 400 mcg of albuterol.

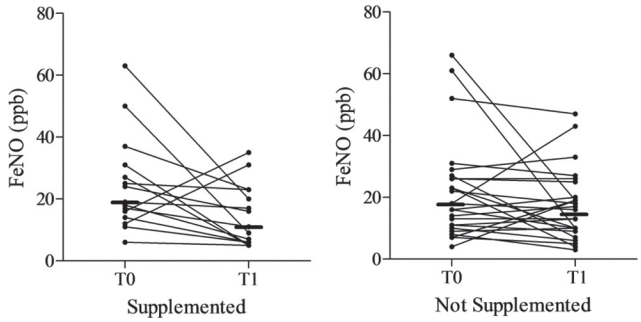

Figure 1. *Median differences of fractional exhaled nitric oxide (FeNO) in supplemented and not supplemented groups.*

RESULTS

None of the children presented with asthma exacerbation during the time considered for the purposes of the present report. None of the children who received the nutraceutical supplement reported adverse events. Lung function and FeNO values before and after supplementation as well as in the control subjects, are reported in Table 2. As can be seen, baseline (T0) and T1 FeNO values did not statistically differ between supplemented and nonsupplemented groups, probably due to the study power calculation. In fact, the study was powered for paired, within groups, T0-T1 analysis, and the number of subjects required for unpaired, between groups, T1-T1 comparison may have required higher number of subjects. After 4 weeks of nutraceutical supplementation, FeNO values decreased significantly, from 19.00 ppb (interquartile range, 14–31 ppb) to 11.00 ppb (interquartile range, 6–23 ppb) ($p = 0.03$). No significant reduction was observed in the control group ($p = 0.13$). Individual FeNO and median values are shown in Fig. 1.

DISCUSSION

In children with asthma, FeNO levels are increased as a consequence of inducible NOS induction by pro-inflammatory cytokines. There is some evidence of the correlation between increased FeNO levels and a high eosinophils level in blood, bronchial biopsy specimens, bronchoalveolar lavage fluid, and sputum, which indicates that FeNO reflects eosinophilic inflammation.[14]

This study showed that supplementation for 1 month with an antioxidant–anti-inflammatory nutraceutical compound was associated with a reduction of FeNO in children with asthma and with mite allergy while temporarily residing in a mite-free environment. This decrease was not related to mite avoidance because it was not observed in children who did not receive antioxidant–anti-inflammatory compounds and the children were already at high altitude for several weeks before the beginning of nutraceutical supplementation. Because, in previous studies,[3,15,16] the decrease in FeNO in relation to allergen avoidance reached a plateau after 2–3 weeks, the observed reduction in this report could be considered somehow additive to what is usually observed with only allergen avoidance in this environment.[3,15,16]

The demonstration of a reduced level of FeNO is important because the reaction of nitric oxide and superoxide anions (O_2^-) in the airway results in the formation of peroxynitrite, a highly reactive oxidant species.[17] Furthermore, FeNO has been shown to be sensitive in detecting oxidative and/or nitrosative stress in airways of patients with asthma, and it is considered together with 8-iso-prostaglandin F2α, a biomarker of the ongoing oxidative and/or nitrosative stress in the airways.[18,19]

In addition, in patients with asthma, it has been shown that FeNO levels inversely correlate with total antioxidant capacity and directly with the plasma level of malondialdehyde, another pointer of oxidative stress.[20] Moreover, a correlation was observed between exhaled hydrogen peroxide and sputum eosinophils, which are known to correlate with exhaled nitric oxide.[21] These findings indicate that inflammation of the

bronchial tree, reflected by increased nitric oxide levels in the airways, is associated with enhanced systemic oxidative stress. No effect of the nutraceutical supplementation was observed in lung function, but this is not surprising because baseline spirometric values were normal.

The supplementation with a compound of nutraceutical (curcumin Meriva, resveratrol, soy phospholipids) elements with anti-inflammatory effects,[22] folic acid,[23] vitamin D,[24] and minerals involved in defense responses and with antioxidant properties, such as zinc, magnesium, and selenium,[25–27] represents a novel approach to the issue of oxidative stress as a determinant of airway inflammation in children with asthma and with allergy.

These results are in agreement with a previous study[28] that documented, in adults with mild-to-moderate persistent asthma, a decrease in eosinophilic airway inflammation and FeNO values after a 4-week period of soy isoflavone dietary supplementation (100 mg/day).[28,29] Furthermore, in an animal model of HDM allergic asthma, resveratrol was shown to reduce tumor necrosis factor α level in bronchoalveolar lavage fluid as well as airway inflammation and remodelling.[30] In addition, resveratrol and quercetin demonstrated *in vitro* nonsteroidal anti-inflammatory activity that may have applications for the treatment of inflammatory diseases.[31] In particular, quercetin, but not deoxyrhapontin, inhibited interleukin (IL) 8 and granulocyte-macrophage colony-stimulating factor release from A549 cells.[31] A549 cell type stimulated by *Dermatophagoides* species extracts altered confluent A549 growth and stimulated the secretion of factors that dysregulate mesenchymal cell growth.[32]

A reduction of eosinophils in the blood was found in adults with asthma who received a higher dose of curcumin[33] but with a lower bioavailability than the one (curcumin–phosphatidylcholine phytosome complex; Meriva)[34]present in the compound we used. In animal models, it was reported that curcumin attenuates allergic airway inflammation by different mechanisms, such as inhibiting B: nuclear factor κ-light-chain-enhancer of activated B cells and its downstream trans-acting T-cell-specific transcription factor[35]; suppressing the activation of signal transducer and activator of transcription 3[36]; and downregulating thymic stromal lymphopoietin, a cytokine implicated in the pathogenesis of allergic diseases, such as asthma, atopic dermatitis, and allergic rhinitis.[37] This natural phenol level was also shown to decrease and prevent lung lesions induced by intestinal ischemia reperfusion injury throughout its antioxidant effect[38] and to block the lipopolysaccharide expression of tumor necrosis factor α, IL-1β, and IL-6, and alleviate airways inflammation in an asthma mouse model.[39]

Moreover, *in vitro* models have shown that curcumin may play a vital role in scavenging nitric oxide, which could prevent bronchial inflammation in patients with asthma[40] and that a curcumin derivate, CNB001, suppresses IL-6, tumor necrosis factor α, IL-1,3 and granulocyte-macrophage colony-stimulating factor in human bronchial epithelium and did so more effectively than did dexamethasone. In this study, the investigators concluded that CNB001 is a promising candidate to treat neutrophilic inflammation and remodeling in asthma.[41] Another possible explanation for the observed effect on FeNO value reduction could be related to the daily administration of vitamin D contained in the supplemented compound. In fact, vitamin D potentiates the effect of inhaled steroids,[42,43] although vitamin status is not a significant determinant of FeNO in children in the general population.[44]

Despite all these plausible biologic explanations for our results, there were some weaknesses in our study, such as its retrospective design, with no placebo-control group and the lack of blood and sputum samples to evaluate markers of eosinophil inflammation and of oxidative stress, such as 8-iso-prostaglandin F2α or malondialdehyde. Furthermore, no evaluation of bronchial hyperactivity was done, which would have provided additional useful information. In fact, in a previous study, magnesium supplementation for 2 months at a dose of 300 mg/day, and thus comparable with that supplemented in our patients, helped to reduce bronchial reactivity to methacholine, to diminish their allergen-induced skin responses, and to provide better symptom control in pediatric patients with moderate persistent asthma.[45] Furthermore, 1 month of supplementation may be too short a period to disclose more significant findings, particularly on air trapping and bronchial hyperresponsiveness; therefore, further and longer studies performed in a double-blind fashion are necessary to confirm our findings. Also, a potential limit of the study may be the difficulty in grading the effect on symptoms because these environmental symptoms improve within few weeks.[46]

CONCLUSION

The results of this study indicated that supplementation with a nutraceutical supplement with antioxidants and anti-inflammatory substances, such as curcumin, resveratrol, soy phospholipids, magnesium, zinc, selenium, and vitamin D, may be associated with reduced airway inflammation as documented by a decrease in the FeNO value in children with asthma and with allergy, and this is in agreement with epidemiologic studies in adults and children that reported beneficial associations between dietary antioxidants and parameters of asthma and atopic disease.[47,48]

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