

Oral magnesium and vitamin C supplements in asthma: a parallel group randomized placebo-controlled trial

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Summary

Background Epidemiological studies suggest that higher intakes of dietary vitamin C and magnesium may be associated with a reduced risk of asthma.

Objective To determine whether vitamin C or magnesium supplements improve the clinical control of asthma in primary care patients.

Methods A randomized, placebo-controlled, double-blind parallel group trial of 16 weeks supplementation with 1 g/day vitamin C, 450 mg/day magnesium chelate or matched placebo. Three hundred patients aged 18–60 years with physician-diagnosed asthma, controlled with at least one dose of an inhaled corticosteroid daily, were recruited from 24 primary care practices in Nottingham, UK. The main outcome measures were change in forced expiratory volume in 1 s, forced vital capacity, airway responsiveness to methacholine, mean morning and evening peak flow, symptom scores and bronchodilator use, both individually and as a combined summary statistic.

Results There was no evidence of any beneficial effect of either supplement on any outcome measure of asthma control in the primary intention-to-treat analysis, or in an analysis restricted to participants who completed the study.

Conclusions Regular dietary supplementation with vitamin C or magnesium adds no clinical benefit to current standard therapy of asthma in primary care patients.

Keywords asthma, magnesium, randomized placebo-controlled trial, vitamin C

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Introduction

Epidemiological evidence suggests that dietary factors may have a significant influence on the incidence and severity of asthma [1]. Vitamin C and magnesium are two nutrients that have been particularly implicated in this respect [2–4], and intervention studies involving single doses or short-term supplementation with vitamin C [5–11] or magnesium [12, 13] have also reported improvements in outcomes such as airflow, exercise-induced bronchospasm and airway hyper-responsiveness. However, there has been only one placebo-controlled study of longer-term use of vitamin C, which reported a decrease in clinical exacerbations of asthma during the rainy season in Nigeria, but did not provide objective data on physiological measurements [14]. A recent review identified the need for large-scale randomized controlled trials to address the effectiveness of vitamin C in patients with asthma [15]. There has been no longer-term study of magnesium supplementation reported to date. We have therefore carried out a randomized placebo-controlled trial to determine whether 16 weeks of regular supplementation with oral

vitamin C or magnesium improves the clinical control of asthma.

Materials and methods

Participants

Patients aged 18–60 years with a physician diagnosis of asthma and using at least one dose of an inhaled corticosteroid daily for the last 6 months were identified from computerized records in 24 General Practices in Nottingham, and sent a written explanation and invitation to participate in the study. Responders were contacted by telephone, and those who were currently taking oral corticosteroids or diuretics, had used vitamin C, magnesium or calcium supplements within 3 months, had experienced exacerbation of asthma within 4 weeks, had a cumulative smoking history of 10 pack years or more, or were pregnant or planning a pregnancy were excluded. The remainder was invited to attend for assessment, and consenting individuals entered a 3-week run-in period. Participants who complied with the measurement protocol and experienced no exacerbation of asthma during the run-in period then proceeded into the supplementation study. The study was approved by Nottingham City Hospital Research Ethics Committee.

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Study design

This consisted of double-blind, randomized, parallel-group comparison of 16 weeks daily oral supplementation with vitamin C, magnesium or placebo. Participants were assigned using a random number generator, in blocks of 9 U, to vitamin C 1 g/day (5.6 mmol) plus magnesium placebo, magnesium amino chelate (Lamberts Health Care, Tunbridge Wells, UK) 450 mg/day (27.6 mmol) plus vitamin C placebo, or double-matched placebo. Randomization was stratified by a regular corticosteroid dose, defined as low or high, the low dose being less than or equal to 1000 µg beclomethasone, 1000 µg budesonide, or 500 µg fluticortide daily. All randomization, tablet preparation and dispensing were carried out independently from the recruitment and assessment of participants. The randomization code was broken at the end of the study or at withdrawal.

Outcome measures

At the beginning and after 4, 8, 12 and 16 weeks of supplementation, we measured 1-s forced expiratory volume (FEV₁), forced vital capacity (FVC), inhaled dose of methacholine causing a 20% fall in FEV₁ (PD₂₀) by the method of Yan et al. [16] to a maximum dose of 12.25 µmol methacholine (and values above this were censored), and average morning and evening peak flow, average daily bronchodilator use and daily symptom score recorded in a diary for the preceding 2 weeks. Our primary outcome measure was change between weeks 0 and 16 in a single summary statistic based on that described by Sears et al. [17], which combined categorical changes in all of the seven above measures, with equal weight given to each outcome (–1 for worse, 0 for same and +1 for better asthma control). Secondary outcomes comprised change in each individual measure.

FEV₁ and FVC were measured using a Vitalograph 2120 spirometer (Vitalograph, Buckinghamshire, UK), taking the higher of two successive measurements within 200 mL for FEV₁, and the best of three technically satisfactory measures for FVC. The peak expiratory flow was recorded as the best of three measurements with a Mini-Wright Peak Flow Meter (Clement Clarke, Harlow, UK) before medication in the morning and evening. Asthma symptoms for the night and day were scored on a scale from 0 (no symptoms) to 5 (incapacitating symptoms). Allergen skin sensitivity to *Dermatophagoides pteronyssinus*, grass pollen and cat fur with histamine and saline controls (Diagenics, Newark, UK) was measured at entry, defining sensitization as an average saline-adjusted skin wheal diameter to any allergen of at least 3 mm. The dietary intake of vitamin C and magnesium was estimated using a semi-quantitative food frequency questionnaire (Diet Q, Tinuviel Software, Warrington, UK), and health status was estimated using the Short Form 36 Health Survey (SF-36™) [18]. Because of a printing error, SF-36 data on physical functioning were incomplete and this section was excluded from analysis. As far as possible, all study visits took place at the same time of day in each individual, after abstaining from short-acting bronchodilator inhalers for 4 h, long-acting bronchodilators for 12 h and antihistamines for 24 h. All regular asthma medications were continued un-

changed. Participants experiencing clinical exacerbation of asthma were treated as considered appropriate by their supervising physician, returning to their regular pre-exacerbation medication use as soon as possible. All participants were asked (but not required) to provide blood for the analysis of serum vitamin C and magnesium levels, and 24 h urine samples for magnesium estimation at the beginning and end of the study. Participants who completed the study were given the option to continue into a controlled corticosteroid reduction protocol; the results of this phase of the study will be reported separately.

Statistical analysis and power

The primary analysis compared changes in the summary statistic between each active treatment and placebo on an intention-to-treat basis, assuming deterioration in all outcomes in participants who withdrew. Changes in the individual measures included in the summary statistic, and in the available SF-36™ data, were analysed as secondary outcomes in participants who completed the study, using parametric or non-parametric tests as appropriate. The effects of adjustment for sex, allergen sensitization, baseline corticosteroid dose, baseline dietary magnesium and vitamin C intake, serum vitamin C and magnesium levels, and 24 h magnesium excretion were assessed using multiple linear regression. Baseline intakes and serum levels were divided into tertiles and interactions with treatment were added to the model to look for effect modification by these baseline variables. We also used linear regression to look at the association between change in serum levels of magnesium and vitamin C, and 24 h urinary magnesium excretion, over the 16 weeks of treatment and a change in the summary score. All analyses were carried out using the Statistical Package for the Social Sciences (version 9.0).

We determined that a sample size of 80 participants per group would provide more than 95% power to detect an average one-point difference in the summary outcome measure, and at least 95% power to detect a 310 mL change in FEV₁ [19], a 20 L/min increase in average peak flow or a 1.5-fold change in airway reactivity relative to placebo. On the expectation of a 20% withdrawal rate, we recruited subjects until a total of 300 had commenced the supplementation period.

Results

Between August 1998 and December 2000, we wrote to 4758 potentially eligible participants and received replies from 1278, all of whom were contacted by telephone to assess eligibility. Of the 573 who appeared eligible and attended for assessment, 323 met the study criteria, and 300 (95 vitamin C, 99 magnesium and 106 placebo) completed the run-in period satisfactorily and entered the study. Baseline characteristics were similar in all groups except for vitamin C intake, which was higher in the group who received vitamin C supplements (Table 1). The 16-week supplementation period was completed by 72 (76%) of those receiving vitamin C, 80 (81%) receiving magnesium and 82 (77%) receiving placebo. The reasons for withdrawal are summarized in Table 2.

Table 1. Baseline characteristics of all participants

	Total	All participants who entered phase 1			Withdrawals
		Vitamin C	Magnesium	Placebo	
<i>Demographics</i>					
Number	300	95	99	106	66
Male (%)	112 (37)	37	33	42	19
Mean age (years) (SD)	41 (11)	42	42	40	39
Mean daily corticosteroid dose (μg) (SD)	646 (506)	715	609	618	618
Number on high-dose corticosteroids* (%)	28 (9)	8	12	8	7
Number on long-acting β-agonists (%)	50 (17)	20	16	14	6
Allergen sensitized (%)	229 (76)	71	78	80	49
Current smokers (%)	12 (4)	5	3	4	4
Mean pack years (SD)	1.3 (2.6)	1.2	1.5	1.1	1.5
Mean dietary magnesium (mg) (SD)	322 (87)	333	317	318	319
Mean dietary vitamin C (mg) (SD)	83 (36)	90	78	82	78
<i>Biological markers</i>					
Mean serum magnesium (mmol) (SD), <i>n</i> = 200	0.8 (0.07)	0.8	0.8	0.8	N/a
Mean 24 h magnesium excretion (mmol) (SD), <i>n</i> = 181	3.5 (1.9)	3.5	3.3	3.4	N/a
Mean serum vitamin C (μmol/L) (SD), <i>n</i> = 200	48.4 (23.3)	53.2	46.2	46.0	N/a
<i>Baseline measures</i>					
Mean FEV ₁ (L) (SD)	2.8 (0.8)	2.8	2.7	2.8	2.7
Mean predicted FEV ₁	87.8 (16.1)	85.3 (15.7)	84.5 (15.1)	83.3 (17.5)	82.9 (15.8)
Mean FVC (L) (SD)	3.7 (1.0)	3.7	3.6	3.8	3.7
Mean log ₁₀ PD ₂₀ (SD)	0.28 (0.73)	0.32	0.32	0.20	0.13
a.m. peak flow (L/min) (SD)	429 (92)	441	418	429	421
p.m. peak flow (L/min) (SD)	438 (91)	445	430	438	439
Daily symptom score (SD)	0.6 (0.7)	0.5	0.7	0.6	0.8
β ₂ -agonist inhaler use (puffs/day) (SD)	2 (2.5)	2.0	2.1	2.1	2.9

*Defined as greater than or equal to 1000 μ g beclomethasone, 1000 μ g budesonide or 500 μ g fluticase daily.
FEV₁, 1-s forced expiratory volume; FVC, forced vital capacity.

Table 2. Reasons for discontinuation of the treatment

	Number of participants		
	Vitamin C group ($N = 95$)	Magnesium group ($N = 99$)	Placebo group ($N = 106$)
Discontinuation at any time (% of those who withdrew)	23 (35)	19 (29)	24 (36)
Asthma deterioration	4	4	4
Disliked tablets	4	3	5
Other medical cause	3	4	5
Non-medical causes (predominantly lack of time)	12	8	10

The intention-to-treat analysis demonstrated no difference in change in the summary statistic relative to placebo with vitamin C (mean difference relative to placebo = +0.06, 95% CI -0.98 to +1.10) or magnesium (mean difference = +0.31, 95% CI -0.69 to +1.30, Table 3). Exclusion of data from the 66 participants who withdrew from the study and in whom all measures were assumed to have deteriorated in the intention-to-treat analysis made no appreciable difference to this result (mean change relative to placebo for vitamin C = -0.1, 95% CI -1.0 to +0.9, and for magnesium = +0.1, 95% CI 0.8 to +1.0). There was no evidence of an interaction between the effect of treatment, and either baseline serum or 24 h urinary excretion for either vitamin C or magnesium.

Blood and urine samples were provided at baseline and after 16 weeks by 200 and 151 participants, respectively. In participants allocated to magnesium, serum magnesium increased from a baseline of 0.8 mmol/L (SD 0.07) by 0.02 mmol/L (95% CI -0.003 to +0.04), and 24 h urine magnesium excretion from 3.5 mmol (SD 1.9) by 1.2 mmol (95% CI 0.3–2.01) relative to placebo with no change in serum vitamin C. In those receiving vitamin C supplements, serum vitamin C increased from a baseline of 53.2 μ mol/L (25.8) by 30.2 μ mol/L (95% CI 21.2–39.2) compared with placebo, with no change in serum magnesium or urinary magnesium excretion. There was no evidence of a relationship between change in the summary statistic, and change in serum vitamin C or 24 h urinary magnesium excretion, while an

Table 3. Effect of 16-week treatment with vitamin C and magnesium on primary and secondary outcome measurements of asthma

Outcome	No	Value	Mean difference from placebo	95% CI of difference	P-value
<i>Primary outcome*[†]</i>					
Single summary statistic	95	Vitamin C: -1.6	+0.1	-1.0 to +1.1	0.91
	99	Magnesium: -1.3	+0.3	-0.7 to +1.3	0.54
	106	Placebo: -1.6			
<i>Secondary outcomes‡</i>					
Change in FEV ₁ (mL)	72	Vitamin C: -48	-11	-92 to +70	0.78
	80	Magnesium: -19	+18	-56 to +93	0.63
	82	Placebo: -37			
Change in FVC (mL)	72	Vitamin C: -36	+7	-127 to +142	0.91
	80	Magnesium: +4	+47	-94 to +191	0.52
	82	Placebo: -43			
Change in PD ₂₀ log 10§	72	Vitamin C: -0.01	-0.15	-0.29 to -0.01	0.04
	80	Magnesium: -0.01	-0.14	-0.29 to 0.0	0.07
	81	Placebo: +0.13			
Change in a.m. peak flow (L/min)¶	72	Vitamin C: +8.0	+0.9	-11.8 to +13.5	0.89
	79	Magnesium: +9.0	+1.9	-10.0 to 13.7	0.76
	81	Placebo: +7.2			
Change in p.m. peak flow (L/min)¶	72	Vitamin C: +9.7	+2.2	-10.0 to 14.3	0.73
	79	Magnesium: +6.1	-1.4	-11.8 to +9.0	0.79
	81	Placebo: +7.6			
Change in symptoms¶, **	72	Vitamin C: 0.0		-0.2 to +0.1	0.33
	79	Magnesium: -0.1		-0.4 to 0.0	0.52
	81	Placebo: 0.0		-0.4 to 0.0	
Change in bronchodilator (puffs/day)¶, **	72	Vitamin C: 0.0		-0.6 to +0.1	0.83
	79	Magnesium: -0.1		-0.6 to +0.1	0.36
	81	Placebo: 0.1		-0.4 to +0.2	

*Intention-to-treat analysis in all who entered the study. †Assuming deterioration in all seven component measures of asthma control in those who did not complete the study. ‡Analysis limited to those who completed the study. §One participant missing as second methacholine challenge not completed due to coughing.

¶Analysis by the Mann-Whitney test with median change and interquartile data presented. **Two peak flow diaries missing. FEV₁, 1-s forced expiratory volume; FVC, forced vital capacity.

increase in serum magnesium was associated with a decrease in the single summary statistic (-0.14 per mmol/L, 95% CI -12.44 to -0.20). Adjustment for these variables, or for sex, atopy or baseline corticosteroid dose, had no effect on any outcome. There was also no difference in change in any of the individual outcome measures with either vitamin C or magnesium relative to placebo in these participants (Table 3). This was also the case if the analysis was restricted to those who consumed less than the median intake of vitamin C or magnesium. There was no evidence of a difference in health status between the groups after 16 weeks treatment as measured by the available SF-36 data.

Discussion

This study was designed to determine whether asthma control in primary care patients using regular inhaled steroids could be improved by supplementation with vitamin C or magnesium, and our entry criteria were deliberately inclusive to ensure that our participants were generally representative of primary care patients with asthma. As in many asthma studies, we collected data on multiple endpoints, and therefore to avoid problems arising from multiple hypothesis testing, we followed a previous example of using a summary

score [17] to combine information from all of these endpoints into a single outcome measure. Our findings are unequivocal, however, in demonstrating no evidence of any benefit, either in relation to this summary score or to any of the individual component measures, in these participants with chronic stable asthma.

Our validation data suggest that the supplements given were sufficient to increase 24 h urinary magnesium excretion by 34% and serum vitamin C by 57%, so it is unlikely that our negative findings are attributable to inadequate supplementation. Our finding is also not attributable to low study power, since we determined our sample size to detect predetermined clinically relevant improvements in the summary statistic and in the major component measures of airflow and airway responsiveness. It is unlikely that the duration of supplementation was insufficient, since previous intervention studies have reported evidence of a benefit after single or short-term repeated doses [6, 9, 10, 12, 20], and our blood and urine monitoring data indicate that participants adhered to the supplementation regime. We therefore conclude that our findings represent a true negative in the context of these primary care patients.

This finding conflicts with the available epidemiological and some short-term intervention trial evidence relating to vitamin C [2, 3, 21-25] and magnesium [3, 4, 12, 13], and implies that the evidence of benefit reported in epidemiolo-

gical studies may have arisen from confounding, possibly by other dietary effects, since intakes of both vitamin C and magnesium are closely related to other nutrients found in fruits and vegetables such as flavonoids and carotenoids. Alternatively, it is possible that supplementation is effective only in subjects with a low baseline intake of these nutrients, and that the lack of effect in our study arises from the fact that baseline daily intakes in our participants were relatively high. However, restricting analysis to those who consumed less than the median intake for the study did not provide any evidence that this actually influenced our findings (data not presented). It is difficult to reconcile our consistently negative results with the preceding smaller studies that demonstrated a benefit over a shorter time with smaller numbers of subjects, and it may be that previous positive reports arise from publication bias in this area. The most likely explanation for our findings is perhaps that our participants were already well controlled on conventional asthma medication, and under these circumstances nutrient supplementation had nothing to add.

Vitamin and mineral supplementation is becoming increasingly common in the UK, and there is a popular belief that such supplements may improve health. Our study suggests that in relation to chronic stable asthma, vitamin C and magnesium have nothing to offer. Further studies are required to determine whether other nutrients associated with vitamin C and magnesium in the diet, or foods rich in these nutrients, can be applied to clinical benefit in this disease.

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