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WHY DON'T WE GIVE CHEST PATIENTS DIETARY ADVICE?

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Introductory article

Dietary vitamin E, IgE concentrations, and atopy

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*Vitamin E inhibits IgE responses to allergic stimuli in animals. We investigated the relation between dietary vitamin E intake and serum IgE concentrations and atopy, measured as allergen skin sensitisation, in a random sample of 2633 adults. Higher concentrations of vitamin E intake were associated with lower IgE concentrations and a lower frequency of allergen sensitisation. These findings may explain the beneficial effect of dietary vitamin E on the incidence of asthma. (**Lancet** 2000;356:1573–4)*

INTRODUCTION

The introductory article by Fogarty and colleagues showed what at first glance might be thought an implausible association.[1] Is it likely that what we eat as adults can have any bearing on what is widely regarded as a genetically determined propensity to allergic disease? The answer is yes. In this paper we shall review the now quite extensive literature on associations between diet and obstructive airway diseases and point to intriguing new evidence that an unbalanced diet may be an important determinant of allergic disease. From this it follows that we should, as chest physicians, pay more attention to what our patients eat.

There is good evidence that oxidant/antioxidant imbalance is important in the pathogenesis of chronic obstructive pulmonary disease (COPD); cigarette smoke contains oxidants and free radicals that, by generating oxygen radicals, damage cellular lipids, proteins and nucleic acids. The neutrophils and macrophages associated with the COPD inflammatory response also release oxygen radicals.[2] These radicals have been implicated in the pathogenesis of COPD because of their ability to induce oxidative inactivation of antiproteinases, tissue damage, sequestration of neutrophils, and the generation of inflammatory mediators. However, other factors must influence the development of COPD because individuals vary in their susceptibility to the effects of cigarette smoke; only a proportion of smokers (15–20%) develop the condition and differences in tobacco consumption do not explain observed international variations in COPD mortality.[3] While individual susceptibility in smokers almost certainly has a genetic component, recent studies have demonstrated protective effects of certain dietary antioxidant vitamins and co-factors.

The rationale for investigating associations between dietary antioxidant intake and COPD derives from pathological considerations, whereas observational epidemiological considerations have stimulated investigations of dietary antioxidant intake and asthma. Asthma and atopic diseases have increased in prevalence since the 1970s,[4–13] and clearly such rapid increases cannot be attributed to alterations in genetic susceptibility; rather, changes in the environment and/or lifestyle must be responsible. In 1994 we argued that the increases in asthma and atopic diseases could not be attributed to air pollution, cigarette smoking, or allergen exposure.[14] Noting that the increase in these diseases had coincided with documented reduction in the intake of fresh fruit and vegetables in the UK, we hypothesised that a westernised diet increasingly deficient in antioxidant vitamins and co-factors had resulted in a shift in population susceptibility, explaining the large increase in disease prevalence. Oxidative stress has been identified in the inflamed airways of asthmatics,[15] with eosinophils, alveolar macrophages, and neutrophils from asthmatic subjects demonstrating enhanced release of reactive oxygen radicals into the tissues. These reactive oxygen radicals seem to play a key role in asthma, directly inducing airway smooth muscle contraction, stimulating mast cell degranulation and epithelial mucus secretion, and possibly interacting with α_1-antiprotease inhibitor.[15]

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Pulmonary antioxidants

Pulmonary antioxidant defences and their relationships with circulating antioxidants are complex and incompletely understood. Studies of lung lining fluid obtained by bronchoalveolar lavage (BAL) indicate that important local antioxidants in the airways include ascorbic acid (vitamin C), α-tocopherol (vitamin E), glutathione and proteins including albumin, caeruloplasmin, and transferrin.[16 17] Water soluble vitamin C provides intracellular and extracellular aqueous phase antioxidant capacity, primarily by scavenging oxygen free radicals,[18 19] and suppresses macrophage secretion of superoxide anions.[20] In humans, lipid soluble vitamin E is the principal defence against oxidant induced membrane injury.[21 22] Lipid soluble β-carotene acts as a free radical scavenger.[21 23] Selenium is an essential co-factor for glutathione peroxidase, an enzyme that plays an important role in antioxidant defences by removing lipid damaging oxygen radicals such as peroxide, lipid, and phospholipid hydroperoxides generated in vivo by free radicals, and other oxygen derived species.[24 25] The in vivo antioxidant effects of vitamins C and E are not independent because kinetic studies indicate an intracellular interaction whereby membrane bound oxidised vitamin E is regenerated non-enzymatically by ascorbate at the membrane-cytosol interface.[26]

The interpretation of studies investigating pulmonary antioxidant defences is difficult because of marked species differences (at least between humans, guinea pigs, and rats) in BAL fluid and cellular antioxidants. Furthermore, within the lung local patterns of antioxidant defence may differ between sites.[27] Pulmonary antioxidant defences change dynamically in response to environmental exposures and disease processes. Human BAL fluid ascorbic acid is consumed during exposure to oxidants such as nitrogen dioxide[28 29] and ozone.[30] Plasma antioxidant capacity falls during acute exacerbations of COPD and asthma, probably reflecting depletion by oxidative stresses, although how this relates to local effects within the lungs is unknown.[31] Extracellular/serum antioxidant levels may not reflect the intracellular milieu, alveolar macrophages from smokers having a higher total ascorbate content and an increased ability to accumulate ascorbate in vitro.[20] Human neutrophils also appear to maintain high intracellular ascorbate to preserve the reducing capacity of the cell at the expense of plasma ascorbate levels.[32] Similar dynamic changes in pulmonary vitamin E levels have been shown in animals, the lungs of animals chronically exposed to smoke having concentrations 2–3 times those of controls, reflecting increased uptake and/or mobilisation of body stores.[33]

Epidemiological studies of dietary antioxidants and airway disease

Epidemiological investigation of dietary antioxidant status is beset by a number of methodological difficulties. Most studies have estimated dietary antioxidant intake by means of food frequency questionnaires enquiring about "portions" of food. Food frequency questionnaire data are used in conjunction with food composition tables to derive semi-quantitative estimates of intakes of individual nutrients such as the major natural antioxidant vitamins. Although the derived intake estimates correlate with weighed dietary intakes, the strength of the associations suggests that the inherent accuracy of this method is relatively low.[34 35] It is therefore common practice to rank estimates of intake and to analyse intake in tertiles/quartiles/quintiles. Nevertheless, the magnitude of any association between estimates of dietary intake and disease outcome tends to be underestimated because the misclassification of diet with respect to outcome is usually random. For some important naturally occurring antioxidants—for example, flavonoids—food composition tables are not yet available or are unreliable because of geographical variation in soil—and hence food—composition of trace elements such as selenium.

Epidemiological studies of dietary antioxidants are also beset by the problem of confounding because foods and diets rich in one antioxidant tend to be rich in others.[36] Smoking is associated with both respiratory symptoms and reduced intake of antioxidants and there is also evidence to suggest that dietary habits may change as asthma develops.[37] An alternative approach to characterising antioxidant status is to quantify blood concentrations of vitamins C, E, A, β-carotene, and the antioxidant trace element selenium (or its functional equivalent glutathione peroxidase). How these blood concentrations relate to intracellular and pulmonary antioxidant status is not clear. These difficulties and methodological limitations should be borne in mind when interpreting results of epidemiological studies of dietary antioxidants and airway diseases.

Observational studies

The associations between dietary antioxidants and parameters of airway disease outlined below are, unless specifically highlighted, those reported after suitable adjustment for the influences of possible confounding factors.

Vitamin C

Dietary vitamin C intake has been associated with ventilatory function, airway reactivity, bronchitis, and wheezing syndromes. In a cross sectional study of 2633 adults aged 18–70 living in Nottingham, ventilatory function was positively related to mean daily intake of vitamin C. A standard deviation increase in vitamin C intake (40.2 mg) was associated with a 25 ml increase in forced expiratory volume in 1 second (FEV_1) and a 23 ml increase in forced vital capacity (FVC).[36] Vitamin E was positively associated with ventilatory function and vitamin C intake but, after adjustment for vitamin C intake, the association between ventilatory function and vitamin E disappeared. A US study of 2526 subjects aged 30–70 in the First National Health and Nutrition Examination Survey (NHANES 1) showed that dietary vitamin C intake was positively associated with FEV_1.[38] There was a mean 40 ml difference in FEV_1 between subjects with the highest and lowest tertiles of vitamin C intake. Dietary intake of vegetables rich in vitamin C was not associated with FEV_1. NHANES 3 related dietary and serum antioxidant status to ventilatory function in 16 693 adults aged ⩾17 years. Serum levels (but not dietary intake) of vitamin C were positively associated with FEV_1, with a standard deviation (4 mg/l) increase in serum vitamin C being associated with a 17 ml increase in FEV_1.[39] In a cross sectional study of 835 men aged 45–75, Ness *et al*[40] showed that serum levels of vitamin C were positively associated with ventilatory function; however, a similar trend in 1025 women was not statistically significant. The Dutch MORGEN study was a cross sectional investigation of 5744 adults aged 20–59. Dietary intake of vitamin C was again positively associated with ventilatory function, but there were no consistent associations with wheezing symptoms.[41] The adjusted FEV_1 of subjects with 90th centile vitamin C intakes was 53 ml greater than in subjects with 10th centile vitamin C intakes, and the difference in adjusted FVC was 79 ml. In

this study, however, there were no associations between dietary vitamin E intake and ventilatory function or wheezing symptoms. The NHANES 2 protocol included detailed dietary and respiratory health assessments in 9074 adults aged ⩾30 years.[42] Serum vitamin C levels were negatively associated with doctor diagnosed bronchitis and with the 12 month period prevalence of frequent wheezing in the absence of infection, but dietary intake of vitamin C was not. In a univariate analysis dietary vitamin C intake was negatively associated with bronchitis, and in the multivariate analysis serum but not dietary vitamin C levels remained significantly associated.

In our own first case-control study the dietary intakes of 51 cases of mean age 36.6 with methacholine airway reactivity were compared with 38 controls of mean age 38.3.[43] Dietary vitamin C intake was negatively associated with airway reactivity. When compared with the highest tertile of vitamin C intake, the lowest tertile of intake was associated with a sevenfold increase in the likelihood of airway reactivity. In a second local nested case-control study of adults aged 39–45 years, 94 cases of adult onset wheeze were compared with 203 controls.[44] These individuals had all denied childhood wheeze when interviewed in 1964 aged 10–14 years. Serum vitamin C levels were negatively associated with adult onset (aged >15) wheeze, a similar trend of borderline significance being noted for dietary vitamin C intake. The association between vitamin C (serum levels and intake) was most pronounced in smokers from the manual social classes.

Vitamin E

Dietary vitamin E intake has been associated with ventilatory function and wheezing syndromes. Dow *et al*[45] investigated 188 adults aged >65 and showed that dietary vitamin E intake was positively associated with ventilatory function, an increase in dietary vitamin E intake of 1 mg being associated with a 42 ml increase in FEV_1 and a 53 ml increase in FVC. Total fruit or vegetable intake did not account for the association between ventilatory function and vitamin E, nor was there an association between vitamin C intake and ventilatory function. Butland *et al*[46] investigated the association between diet and ventilatory function in a prospective study of 2512 Welsh men aged 45–59. Cross sectional analysis showed that dietary vitamin E intake was positively associated with FEV_1, a standard deviation (2 mg/day) increase in vitamin E intake being associated with an increase in FEV_1 of 32 ml. Longitudinal analysis indicated no significant association between change in FEV_1 over a 5 year period and change in dietary vitamin E intake or mean dietary vitamin E intake. In this study there were no associations between dietary vitamin C intake and ventilatory function. As part of the Seven Countries Study protocol, data on ventilatory function and diet were collected in Finland, Italy, and the Netherlands.[47] In the Finnish arm 1248 adults aged 50–69 were studied. Dietary vitamin E intake was positively associated with FEV_1, a standard deviation increase in vitamin E intake of 35 mg/day being associated with an increase in FEV_1 of 93 ml. There were no similar associations in the other two study centres. NHANES 3 also demonstrated that dietary vitamin E intake was positively associated with FEV_1, a standard deviation increase in dietary vitamin E intake (α-tocopherol 9 equivalents/day) being associated with an increase in FEV_1 of 11.5 ml.[39] Similarly, serum vitamin E levels were positively associated with FEV_1, a standard deviation increase of 4.9 mg/l being associated with a 39.2 ml increase in FEV_1.[39]

In our own second case-control study dietary vitamin E intake was negatively associated with adult onset wheeze.[44] A negative association was also found between adult onset wheeze and serum α-tocopherol levels (adjusted for serum triglycerides).[44] When compared with the highest tertile of vitamin E intake, the lowest tertile of intake was associated with a fourfold increase in the likelihood of adult onset wheeze. In the same study, highly atopic individuals—as defined by three positive allergen skin prick tests—demonstrated a threefold increase in the likelihood of adult onset wheeze compared with non-atopic individuals, which was comparable with the risk associated with a low vitamin E intake. As with the association between vitamin C and adult onset wheeze, the associations between adult onset wheeze and dietary vitamin E intake or serum α-tocopherol levels were most pronounced in smokers from the manual social classes. In a further study, this time of 12 year old Saudi Arabian children, we compared 114 children with a history of asthma and wheeze in the previous 12 months with 202 classroom controls.[48] Dietary intake of vitamin E was negatively associated with asthma and wheezing. When compared with the highest tertile of vitamin E intake, the lowest tertile of intake was associated with a threefold increase in the likelihood of asthma and wheezing. This was comparable to the increased likelihood of asthma and wheezing associated with atopy, as determined by a positive allergen skin prick test. The US Nurses' Health Study[37] followed 77 866 women aged 30–55 years prospectively for 10 years. The incidence of physician diagnosed asthma was negatively associated with dietary intake of vitamin E, the highest quintile of intake being associated with a 47% reduction in the likelihood of developing asthma when compared with the lowest quintile of vitamin E intake. This association was only valid for dietary intake of vitamin E excluding supplementation and was only demonstrable if dietary vitamin E intake had been characterised in the previous 2 years, suggesting that, for asthma, recent dietary intake of vitamin E may be more important than past intake. In the Nurses' Health Study there were no associations between dietary vitamin C intake and the likelihood of developing physician diagnosed asthma.

Associations between dietary antioxidant intake and asthmatic phenotype were investigated by Baker *et al*[49] who used 5 day weighed intakes in 20 patients with brittle asthma (mean age 49.4), 20 with non-brittle asthma (mean age 49.9), and 20 healthy adults (mean age 49.3). Dietary vitamin E intake was significantly lower in patients with brittle asthma than in those with non-brittle asthma and in normal adults. Serum vitamin E levels exceeded the normal range in all subjects, but these levels were higher in the patients with brittle asthma than in those with non-brittle asthma and in normal subjects. This paradox may have arisen because of failure to adjust serum vitamin E levels for serum lipids or the previously reported disparity between pulmonary and serum antioxidant levels. The measurement of biologically functional serum vitamin E levels is difficult because of its complex association with serum lipids; adjustment of serum vitamin E for serum triglycerides and/or cholesterol has been recommended.[50]

β-carotene

Several studies have investigated relations between retinol or β-carotene and respiratory disease. Retinol is not usually considered to be an antioxidant, and the following discussion is limited to the antioxidant retinol precursor, β-carotene. NHANES 3 demonstrated that dietary intake of β-carotene was positively associated with FEV_1, a standard deviation

increase in dietary β-carotene intake (1017 retinol equivalents or approximately one raw carrot/day) being associated with a 16.1 ml increase in FEV_1.[39] A similar negative association was also seen between serum β-carotene level and FEV_1, a standard deviation increase in serum β-carotene of 210 µg/l being associated with a 12.5 ml increase in FEV_1.[39] In NHANES 3 both of the associations between β-carotene and ventilatory function were weaker in current smokers. The Carotene and Retinol Efficacy Trial (CARET) included 706 men aged 45–74 years with occupational asbestos exposure.[51] There were no associations between dietary β-carotene intake and ventilatory function, but serum β-carotene levels were positively associated with ventilatory function. The difference between the 25th and 75th centiles of serum β-carotene levels (155 ng/ml) was associated with a 90 ml increase in FEV_1 and an 82 ml increase in FVC. The MORGEN study demonstrated conflicting associations between dietary β-carotene intake and parameters of airway disease. Dietary β-carotene intake was positively associated with ventilatory function, the FEV_1 of subjects in the 90th centile of β-carotene intake being 60 ml higher than that of subjects in the 10th centile. Similarly, the difference in FVC between these two levels of β-carotene intake was 75 ml. However, there was a significant positive association between β-carotene intake and the 12 month period prevalence of wheeze in the absence of infections, suggesting an adverse effect of dietary β-carotene intake.[41] It was suggested that these contradictory associations with β-carotene might have been a consequence of reporting bias, changes in the diet of subjects with respiratory symptoms, or because a lag period between the possible protective effects of β-carotene on ventilatory function differs from that for respiratory symptoms. Analysis of data from the Dutch arm of the Seven Countries Study[47] showed that dietary β-carotene intake was positively associated with FEV_1, a standard deviation increase in β-carotene intake of 0.4 mg/day being associated with a 56 ml increase in FEV_1. There were no similar significant associations in the Finnish and Italian arms.

Selenium

This key trace element is a co-factor of glutathione peroxidase, an enzyme that plays a key role in protecting cells against oxidative damage. NHANES 3 demonstrated that serum selenium levels were positively associated with FEV_1, a standard deviation increase in serum levels of selenium of 17 ng/ml being associated with an increase in FEV_1 of 25 ml.[38] Stone *et al*[52] conducted a case-control study in 49 subjects with symptomatic asthma (mean age 33.3) and 76 normal healthy controls (mean age 38.9). The asthmatic patients had significantly lower concentrations of plasma and whole blood selenium. No significant differences were apparent for platelet selenium and glutathione peroxidase or whole blood glutathione peroxidase. The lowest concentrations of plasma and whole blood selenium were associated with increases of 3.5-fold and 5.1-fold, respectively, in the likelihood of asthma when compared with the highest concentrations. A similar case-control study in New Zealand compared the selenium status of 56 asthma patients (mean age 39) and 59 healthy controls (mean age 37).[53] The whole blood selenium and glutathione peroxidase levels in the asthmatic subjects were significantly lower than in the non-asthmatic controls. The lowest whole blood concentrations of selenium and glutathione peroxidase were associated with 1.9-fold and 5.8-fold increases, respectively, in the likelihood of asthma when compared with the highest concentrations.

Fruit

The studies outlined above have characterised dietary antioxidant intake by the content of individual vitamins and trace elements. By its very nature, this form of analysis is crude, limited to what can be easily estimated, and overly simplistic because the antioxidant content of the food does not only comprise vitamins C, E, and β-carotene. Important influences may be exerted by other potent antioxidants such as the flavonoids, and many trace elements are co-factors for antioxidant enzymes—for example, iron, manganese, zinc, and copper. Our original hypothesis emphasised the association between trends in fruit and vegetable consumption and the recent increase in asthma, and the declining antioxidant content associated with the reduction in fruit and vegetable consumption was proposed as a plausible biological explanation for the increase.[14] Although studies of respiratory disease and dietary fruit intake may superficially appear crude, they provide pragmatic data and probably point the way for future preventative public health interventions. Fruit intake does not appear to be a surrogate for vitamin C, E, and β-carotene intake because many of the associations with respiratory disease are independent of these vitamins. Fruit intake may be a surrogate for a healthy diet, or for antioxidants other than vitamin C, E, and β-carotene which may be more pertinent.

The study of Welsh men[46] indicated that frequent consumption of apples was positively associated with FEV_1. The FEV_1 of subjects consuming ⩾5 apples a week was 138 ml greater than that of subjects who never ate apples, this association being stronger than that between vitamin E intake and FEV_1. This study did not support the hypothesis that the observed association between apples and ventilatory function was a consequence of the vitamin C content of apples. Not only was the association between apples and FEV_1 independent of the intake of vitamins C and E, but there was also no association between FEV_1 and intake of vitamin C or other food sources rich in vitamin C. The Italian arm of the Seven Countries Study demonstrated that fruit consumption was positively associated with FEV_1, a standard deviation increase in fruit consumption of 180 g being associated with an increase in FEV_1 of 68 ml. There were no similar associations in the Finnish and Dutch arms.[47] The Health and Lifestyles Study (HALS) included quantification of dietary intake of fruit and ventilatory function in British adults aged 18–73 in 1984. In a cross sectional study of 2859 subjects, winter consumption of fresh fruit or fruit juice was positively associated with FEV_1.[54] The FEV_1 of subjects consuming fresh fruit/juice in the winter was 78 ml greater than that of subjects whose winter fruit consumption consisted of no fruit juice and fresh fruit less than once a week. A second HALS in 1991 enabled a longitudinal study of 2171 subjects. In cross sectional analyses of the 1984 and 1991 surveys there were positive associations between fruit consumption and FEV_1, the FEV_1 of subjects consuming fruit daily being 105 ml and 188 ml greater than that of subjects who ate no fruit in 1984 and 1991, respectively.[55] Change in ventilatory function between the two surveys was related to changes in dietary fruit intake rather than the mean fruit intake over the 7 year interval. The authors suggested that the cross sectional effects of fruit consumption on ventilatory function appeared to be reversible and not progressive, with consistently low levels of fruit intake appearing not to increase the rate of ventilatory decline.

Fresh fruit consumption was positively associated with FEV_1 in a study of 2650 children aged 8–11 years from 10

towns in England and Wales,[56] with the FEV_1 of children consuming fresh fruit more than once a day being 88 ml greater than that of children who never ate fresh fruit. There was no association between fresh fruit consumption and wheezing, or between plasma vitamin C levels and FEV_1. In the SIDRIA study of 18 737 Italian children aged 6–7, the winter consumption of citrus and kiwi fruit was negatively associated with wheezing, dyspnoea with wheeze, severe wheeze, exercise induced wheeze, nocturnal cough, and rhinitis.[57] There was no evidence of a dose response, the effect of weekly consumption of 1–2 fruits being similar to the effect of consuming 5–7 portions a week. In the prospective Dutch Zutphen study the incidence of chronic non-specific lung disease (CNSLD) in 763 men was negatively associated with the consumption of solid fruits such as apples and pears.[58] There were no significant associations between CNSLD and dietary intake of vitamin C, β-carotene, and selenium. The NCDS study of 11 352 adults aged 33 years included characterisation of diet and respiratory health.[59] Summer fresh fruit consumption was negatively associated with frequent wheeze and speech limiting attacks of wheezing. It was also found that increasing fruit consumption from never to more than once a day was associated with a 32% decrease in the likelihood of frequent wheezing.

Intervention studies

In contrast to the number of observational studies of dietary antioxidants and airways disease, intervention studies are relatively few in number and have generally failed to assess baseline antioxidant status. A number of small studies have assessed the respiratory effects of dietary supplementation with vitamins C, E, β-carotene, and selenium. Studies supplementing with vitamin C alone have in general produced conflicting results. The administration of 1.0 g of oral ascorbic acid to 14 mildly asthmatic subjects was associated with a reduction in airway reactivity to methacholine 1 hour later.[60] Vitamin C supplementation appeared to exert this effect by influencing arachidonic acid metabolism, since the protective effect of vitamin C supplementation was abolished by co-administration of indomethacin. Administration of 500 mg ascorbic acid to 14 healthy subjects was associated with a reduction in the bronchoconstriction induced by inhaled histamine 3 and 6 hours later.[61] The increase in methacholine airway reactivity induced by inhalation of 2 ppm NO_2 in 11 healthy subjects was abolished by pretreatment with vitamin C (500 mg qds for 3 days).[62] Exercise induced bronchoconstriction in 12 adult asthmatic subjects was significantly attenuated by pretreatment with 500 mg ascorbic acid daily for 2 days.[63]

A number of vitamin C supplementation studies have failed to demonstrate an effect on ventilatory function or airway reactivity. The administration of 2 g ascorbic acid to 16 adult asthmatic subjects was not associated with any change in ventilatory function or histamine airway reactivity.[64] Similarly, in 20 mildly asthmatic subjects, pretreatment with ascorbic acid (2 g daily for 3 days and 1 g on the assessment day) was not associated with any change in ventilatory function.[65] On the other hand, two studies have investigated whether the detrimental effects of ambient ozone exposure on ventilatory function could be ameliorated by dietary supplementation with combined vitamin C (650 mg), vitamin E (75 mg), and β-carotene (15 mg) daily. Romieu *et al* reported the effects of 6 weeks of dietary supplementation with these vitamins in 34 male shoe cleaners exposed to high ozone levels during their work on the streets of Mexico City.[66] The negative association between ozone exposure and FEV_1 and FVC was abolished by the combined vitamin preparation. Similar dietary supplementation of 26 amateur cyclists for 3 months also abolished the association between 8 hour ambient ozone exposure during road cycling and FEV_1, FVC, and PEFR.[67] Dietary selenium supplementation (100 µg sodium selenite) for 14 weeks in 24 asthmatic subjects increased serum selenium and platelet glutathione peroxidase levels and was associated with an improvement in an assembled clinical evaluation of asthma control.[68] However, this overall improvement in asthma control was not associated with significant changes in the individual clinical parameters of ventilatory function and airway reactivity.

Modulation of T helper cell differentiation by antioxidants

Oxidative stress has been identified in the inflammatory processes that characterise asthma and COPD, and most of the literature describing antioxidants and airways disease has concentrated on the antioxidative rather than the immunomodulatory properties of vitamins and trace elements. Although oxidant stress may play a role in established asthmatic airway inflammation, asthma differs fundamentally from COPD in being an immunologically mediated disease.

It is widely accepted that CD4+ T helper (Th) cells play a pivotal role in the initiation and perpetuation of the chronic inflammatory process associated with asthma.[69 70] The immunopathogenesis of atopic disease has also been clarified by the recognition that murine Th cells differentiate into two major functional phenotypes (Th1 and Th2) characterised by their secreted cytokines, and that naïve precursor Th cells are not pre-committed to the Th1 or Th2 lineage. Th1 cells predominantly secrete interleukin 2 (IL-2) and interferon γ (IFN-γ), while Th2 cells predominantly secrete IL-4 and IL-5.[70–73] Human Th1 and Th2 cells produce similar patterns of cytokine secretion, but the secretion of certain cytokines is not so tightly restricted to a single subset as has been demonstrated in mice.[74] Studies of Th cells from blood and BAL fluid indicate that atopic asthma is associated with a bias towards the Th2 phenotype.[75 76] IL-4 is extremely potent in inducing the isotype switching of B cells to the synthesis and secretion of IgE.[77 78] IL-5 promotes eosinophil growth, differentiation, and peripheral activation.

It would appear that there may be subtle differences in the associations between dietary antioxidants and asthma and COPD. The observational studies outlined above suggest that dietary intakes of vitamin C, vitamin E, β-carotene, and fruit appear to exert a protective effect on ventilatory function, whereas vitamin E, selenium and, possibly, fruit appear to exert a protective effect against asthma and wheezing syndromes. These somewhat different associations between antioxidants and asthma/wheezing syndromes, on the one hand, and ventilatory function on the other may be a consequence of general antioxidative effects and also—in some cases, for example, vitamin E and selenium—immunomodulatory influences. Thus, the adverse effects of a diet deficient in antioxidants in patients with COPD may reflect the predominant general antioxidative effects, but in patients with asthma a diet deficient in antioxidants may influence the development of asthma by two mechanisms—firstly, Th cell differentiation towards the Th2 phenotype may be promoted and, secondly, once airway inflammation is established, damaging antioxidant stresses may be exaggerated.

The possibility that a diet increasingly deficient in antioxidants influences Th cell polarisation towards the Th2

Learning points

- The scientific rationale for a protective effect of dietary antioxidants in the pathogenesis of COPD is relatively well established.
- It has been hypothesised that a diet increasingly deficient in natural antioxidants underlies the recent increases in asthma and atopic disease.
- Dietary intake of fruit and the antioxidants vitamin C, vitamin E, β-carotene, and selenium are increasingly being associated with improved ventilatory function.
- Dietary intake of fruit and the antioxidants vitamin E and selenium are increasingly being associated with a reduced prevalence of asthma and wheezing syndromes.
- Dietary antioxidant deficiency may influence the pathogenesis of asthma by both immunomodulatory (promoting Th2 polarisation) and reduced antioxidative mechanisms.
- Further pragmatic research is required to establish the feasibility and efficacy of dietary manipulation as a public health measure to reduce the risk of asthma and atopic disease.

phenotype and thus clinical allergic disease is supported by a limited amount of in vitro work demonstrating that antioxidants can influence the cytokine secretion that is so critical in Th cell differentiation and effector function. N-acetyl-L-cysteine (NAC) is an antioxidant precursor of glutathione; in vitro studies of human lymphocytes have shown that NAC and glutathione increase IL-2 secretion, decrease IL-4 production, and selectively decrease IL-4 induced IgE production in a dose-dependent manner with no effects on IFN-γ, IgM, or IgA production.[79] These findings suggest that NAC and glutathione have the potential to suppress Th cell differentiation towards the Th2 phenotype. In the murine model of HIV, mice infected with the LP-BM5 retrovirus have decreased hepatic and serum levels of vitamin E and this is associated with the Th2 phenotype—namely, increased in vitro IL-4 secretion and reduced IL-2 and IFN-γ production. These changes are reversed by supplementation with pharmacological doses of vitamin E.[80] In another murine model a 15-fold increase in dietary vitamin E restored in vitro thymocyte and splenocyte production of the Th1 cytokine IL-2 and the Th2 cytokine IL-5, but not IL-4, after it had been suppressed by feeding the mice with ethanol.[81] Supplementation of the diet of BALB/c mice with vitamin E reduced in vitro splenocyte proliferation and splenocyte secretion of IL-4 and IL-5.[82] In F344 rats, supplementation of the diet with vitamin E increases the number of thymocytes and their in vitro ability to secrete IL-2.[83] A study of the effects of unsaturated fatty acids (UFA) on the in vitro secretion of IgE by mesenteric lymph node lymphocytes from Sprague-Dawley rats concluded that UFA enhanced IgE secretion but that the mediators of this effect were the oxidative products of UFA. Subsequent in vitro supplementation of the mesenteric lymph node lymphocytes with α-tocopherol inhibited IgE secretion, while supplementation with vitamin C did not influence IgE secretion.[84]

It is therefore biologically plausible that dietary antioxidants not only ameliorate airway inflammatory antioxidant stress, but also (probably more importantly in the immunopathogenesis of asthma) may play a more fundamental role by influencing Th cell differentiation. This modification of our antioxidant hypothesis leads us to predict that dietary antioxidant intake would influence, not only the development of asthma, but also the development of other Th2 associated diseases such as allergic rhinitis and atopic eczema and the markers of atopy, serum IgE, and skin prick tests. The study by Fogarty *et al* (introductory article)[1] is particularly pertinent because it demonstrates for the first time that dietary intake of vitamin E is negatively associated with serum IgE and atopic sensitisation.

Immunological considerations of Th cell differentiation suggest that factors influencing Th cell polarisation at the time of first allergen exposure are potentially disproportionately potent because of natural immunological mechanisms that promote further differentiation towards that phenotype and powerful inhibition of the reciprocal phenotype. It is clear that allergen exposure and Th cell sensitisation occurs during in utero development and during early postnatal life.[85] This raises the possibility that maternal dietary antioxidant intake during pregnancy and breast feeding and infant dietary antioxidant intake may be particularly important in the pathogenesis of asthma and atopic disease. There is some indirect evidence implicating maternal diet during pregnancy and the development of atopic disease in children. Measurements of body length and head circumference at birth have been associated with asthma and atopic disease.[86–90] These measurements are influenced by numerous factors that are complex and vary with gestational age, but include maternal nutrition.[91–95] Maternal dietary antioxidant intake during pregnancy has been indirectly implicated with atopy by Oryszczyn *et al*[88] who found an association between cord blood IgE levels and placental calcification, a feature which had been shown to be associated with low maternal dietary antioxidant intake during pregnancy.[96]

Concluding remarks

It is generally accepted that the oxidant/antioxidant balance plays an important role in the development of COPD, and this is consistent with several epidemiological studies demonstrating positive associations between dietary vitamins C and E and ventilatory function. We have hypothesised that the recent increase in asthma and atopic disease is a consequence of a diet increasingly deficient in antioxidants. An increasing number of epidemiological studies support this hypothesis by demonstrating positive associations between

vitamin E, β-carotene and selenium and ventilatory function, and negative associations between these antioxidants and asthma and wheezing syndromes.

There are probably two mechanisms underlying the association between dietary antioxidant intake and features of asthma. Firstly, the oxidative stresses associated with established asthmatic airway inflammation are probably ameliorated by dietary antioxidants. However, secondly, immunological considerations suggest that antioxidant deficiency may be associated with the Th2 phenotype normally associated with atopic disease. By demonstrating a negative association between dietary vitamin E intake and serum IgE and atopy, the study by Fogarty *et al*[1] is the first in vivo demonstration of this plausible immunomodulatory effect of dietary antioxidants.

We have not discussed the possible roles of fatty acids in this review, but it should be noted that there are important metabolic relationships between vitamins E, C, and fats, and that vitamin E in our diet is obtained from the fat content of a wide range of foods. Further studies are required, particularly with respect to the interactions of antioxidant vitamins and fatty acids and their influence early in life, perhaps in utero, in determining atopic/asthmatic status. There is, however, now a solid body of epidemiological evidence and a plausible biological mechanism for our original hypothesis. The test will come from intervention studies. Future primary preventative public health measures directed against asthma and atopic disease may involve dietary manipulation, but in the meantime it seems not unreasonable to advise our patients of the likely beneficial effects of fruit and vegetables on respiratory health.

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