Dietary Salt Intake as a Potential Modifier of Airway Responsiveness in Bronchial Asthma

TIMOTHY D. MICKLEBOROUGH, Ph.D., 1 and ROBERT W. GOTSHALL, Ph.D. 2

ABSTRACT

While pharmacologic treatment of chronic asthma is usually highly effective, medications often have significant side-effects or exhibit tachphylaxis. Alternative and/or complementary treatments that reduce dependence on pharmacologic medications are of interest in reducing the severity of asthma. This review analyzes the literature that has evaluated dietary salt intake as a potential modifier of the severity of asthma and airway responsiveness. High dietary intakes of salt, greater than 9 g/d, are common in Western civilizations, as is asthma. The question is whether reducing dietary salt intake potentially would improve pulmonary function and airway responsiveness in individuals with asthma. This review details the existing studies in this regard and includes the studies that have evaluated dietary salt on the severity of exercise-induced asthma (exercise-induced bronchoconstriction [EIB]). From a critical analysis of the existing literature, the data that support a role for dietary salt reduction for reducing severity of asthma and airway responsiveness in individuals with asthma is considered encouraging but not clinically convincing. The existing studies have suffered from a variety of experimental and population limitations. In contrast, the data from studies that have altered dietary salt and evaluated severity of EIB in nonatopic individuals is much more convincing. In each study so far, lowering dietary salt has reduced the severity of EIB to subclinical levels. Correspondingly, the supplementing of diets to higher than normal salt intake increased EIB significantly. This review concludes that the data are sufficient to warrant a clinical trial that is properly controlled and randomized to further investigate the influence of dietary salt intake on pulmonary function, airway responsiveness, symptoms, quality of life, and medication requirements in asthma and EIB.

INTRODUCTION

There have been remarkable advances in asthma therapy over the last 10 years. Primarily, inhaled corticosteroids and short-acting $\beta_2$-agonists have proven highly effective as medications in relief of symptoms, and long-acting $\beta_2$-agonists have facilitated the control of asthma. Daily medications such as leukotriene antagonists have recently proven highly effective in asthma therapy. However, these medications are not without real and potential side-effects. Additionally, prolonged use of some medications results in reduced effectiveness, or tachphylaxis. Therefore, alternative therapies for treatment, or therapies that reduce the dose requirements of traditional medications (complementary therapy) would be of benefit to the patient with asthma, and potentially reduce the public health burden of this disease.

Diet has the potential to be involved in the severity of diseases such as asthma by either contributing to the etiology of the disease, or, by serving as a potential modifier of disease severity. In the case of asthma, some dietary components have been investigated as to their potential relationship to the severity of the asthma, and as potential agents

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in improving pulmonary function in individuals with asthma. This review is the first in a series of three reviews that will address specific dietary components, or supplements, and their potential effect in the etiology and/or potential for the treatment of asthma. The purpose of the present review is to provide a critical analysis of the existing information regarding the potential relationship between dietary salt (sodium chloride) intake and the severity of asthma. In particular, the review addresses the question of dietary salt reduction as an alternative or complementary treatment for asthma.

For this review, the keywords salt, dietary salt, and sodium chloride were linked with the keywords asthma, exercise-induced asthma, and exercise-induced bronchoconstriction. Data used were MEDLINE™ and SPORTDiscus. Both human and animal studies were included.

**DEFINITIONS AND PREVALENCE**

Chronic bronchial asthma is an inflammatory disease characterized by airway hyperresponsiveness to a number of different stimuli. In particular, asthmatic airways are obstructed by excess mucous production, bronchiolar smooth muscle contraction, and airway membrane edema. Typically, the triggers for airway obstruction in individuals with asthma include allergens (e.g., dust, mites, pollen, et cetera), smoke, cold air, infectious agents, hyperventilation, and exercise. Clinically, airway responsiveness is assessed to aid in the diagnosis and treatment of asthma. Inhalation of controlled doses of methacholine or histamine are most typically used to determine airway responsiveness by clinicians and there are specific guidelines for this testing provided by the American Thoracic Society (American Thoracic Society, 2000). For methacholine, which is the preferred agent, the American Thoracic Society (American Thoracic Society, 2000). Typically, a greater than 10% decrease in FEV1 postexercise indicates abnormal pulmonary function, and a 15% decrease in FEV1 is diagnostic of EIB (Anderson, 1985) (Table 2). Eighty percent (80%) to 90% of individuals with asthma have EIB, depending on the study (Lacroix, 1999), while the percent of individuals without asthma who have EIB is unknown in the general population. EIB does not typically present a medical emergency nor is it cause for a hospital emergency/admittance, so data on prevalence within the general population are sparse. The best estimate of the prevalence of EIB for the general population is 3%–10% (Rupp, 1996). Estimates range as high as 19.3% in a sample of Australian schoolchildren (Haby et al., 1995). Estimates of EIB for various athletic populations are generally higher. For example, a survey of the 1984 U.S. Olympic team indicated that approximately 11% had EIB (Voy, 1986). More recently, Wilber reported that this prevalence was 23% for the 1998 U.S. Winter Olympic team (Wilber et al., 2000). Thus, the prevalence of EIB is high in the asthmatic population, and likely in significant numbers in those without asthma.

Because solitary EIB (those without asthma with EIB) is considered part of the asthmatic diathesis, it may be a marker of a yet to be expressed chronic asthmatic condition. Understanding EIB may allow earlier detection of asthma and more timely treatment and prophylaxis, particularly because 29%–51% of asthma is silent or undetected unless the subjects exercise (Rupp et al., 1992). For the alert practitioner, EIB provides the ideal opportunity to detect and better manage asthma, which is currently undertreated and underdiag-

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<th>Dose of methacholine for a 20% reduction in FEV1 (PD20)</th>
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<td>&gt; 16 mg/mL</td>
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<td>&lt; 1 mg/mL</td>
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FEV1, forced expiratory volume in 1 second.
nosed. In particular, and for the purposes of this review, the study of EIB may serve as a convenient and useful model for investigation of potential dietary interventions for reducing airway responsiveness.

DIETARY SALT AND ASTHMA

It has been observed that asthma morbidity and mortality are greater in communities adopting a more Western lifestyle and in migrants as they move from rural underdeveloped to urban Westernized areas (Burney, 1987a, 1987b; Mohamed, et al., 1995; Van Niekerk, 1979; Waite, et al., 1980). Dietary intake of sodium chloride is typically high (typically averaging 7–10 g/d; 2.8–4 g/d of sodium) (Dahl and Love, 1957; Sanchez-Castillo et al., 1987) in Westernized areas and this excess salt intake is associated with several diseases and conditions (e.g., hypertension [de Wardener and MacGregor, 2002]). The minimum recommended daily allowance (RDA) for sodium in the United States is 500 mg/d (National Research Council, 1989), and intakes less than 2400 mg of sodium per day are preferred (National Research Council, 1989) for health.

Stoesser and Cook (1938) in 1938 were the first to propose a possible connection between salt consumption and the severity of chronic bronchial asthma. In a study published in abstract form only, in which the number of subjects or other details was not provided, they observed that a low-salt diet contributed to a decrease in symptoms in children with severe asthma, and when given high-salt diets their condition worsened. This study, while lacking in scientific rigor and pulmonary function data, did provide the first indication that dietary sodium chloride might play a role in modifying the severity of asthma.

Epidemiologic and cross-sectional studies

Recognizing the possibility that a high-salt diet may worsen symptoms of asthma (Stoesser and Cook, 1938), Burney (1987a; 1987b) hypothesized that increased sodium intake might, in part, be responsible for the increased morbidity and mortality of asthma observed in Westernized cultures. Burney and colleagues (1986) tested the hypothesis using regional asthma death rates and regional table salt purchases from England and Wales. They found a strong correlation between table salt purchases and mortality because of asthma in men and in children of both genders, but not in women. The suggestion from these data was that higher dietary sodium chloride may potentiate asthma severity. The failure to demonstrate a potential link in the case of women was presumed by the investigators to be to misclassification of women with bronchitis as asthmatic.

In a subsequent study, Burney and colleagues (1989) conducted a cross sectional survey of the prevalence of asthma in rural and urban areas in the south of England. A random 20% of those men who replied, including all those who responded that they had symptoms of asthma, were tested for airway hyperresponsiveness with histamine challenge and for atopy with allergen skin tests. A total of 205 men (18–24 years of age), of which 138 men had 24-hour urine specimens, underwent the histamine challenge test. The geometric mean of the 24-hour sodium excretion for those men who had airway hyperresponsiveness (n = 43) was 4163 mg of sodium per day; while that for those men who had normal airway responsiveness (n = 95) was 3841 mg of sodium per day. This difference was not statistically significant (0.10 < p < 0.20). Regression analysis found increased 24-hour urinary excretion of sodium, but not potassium, to be significantly associated with airway responsiveness to histamine.

Factors associated with bronchial reactivity such as age, smoking, and skin sensitivity were considered in the analyses. Thus, the authors concluded that a high-sodium diet may potentiate bronchial reactivity, although other uncontrolled dietary factors may have been confounding. The range of sodium consumption rates reported was within the typical rates of intakes considered excessive, but usual for a Western diet. The lower sodium excretions presented here, 3841 mg/d, are typical for the Western diet and not representative of a low-salt diet (below 2400 mg/d). Thus, it is of some importance that airway responsiveness was increased across this already excessive range of dietary sodium intakes.

Schwartz and Weiss (1990) used information collected in the Second National Health and Nutrition Examination Survey (NHANES II) for potential relationships among dietary factors and respiratory symptoms. The population examined was 9074 white and black adults 30 years of age and older. Dietary factors were derived from serum levels and from 24-hour dietary recall questionnaires. From these instruments it was estimated that the sodium intake was 2640 mg/d and the potassium intake was 2334 mg/d. The sodium–potassium ratio was 1.25 on average. The analysis indicated that while neither sodium nor potassium was individually related to bronchitis or wheezing symptoms, the dietary ratio of sodium to dietary potassium was a significant predictor of bronchitis as reported by these adults. Considering the fact that individuals were on their usual diet and that the data were self-reported, the relationships found in this study cannot be considered as convincing. However, these data do contribute to the body of evidence suggesting dietary electrolytes may contribute to airway responsiveness.

Pistelli et al. (1993) performed a cross-sectional study in Italy among 2593 subjects 9–16 years of age. Questionnaires were used to determine table salt use, asthma, and asthma symptoms such as wheezing and coughing. Personal table salt use was positively correlated with reported symptoms of asthma, and was found mainly in boys, not in girls. A subset (n = 2020) of subjects underwent methacholine challenge and 910 subjects collected a morning urine sample for electrolyte analysis. Airway responsiveness was positively associated with urinary potassium excretion in boys but not...
with urinary sodium excretion. Thus, while table salt use was related to symptoms of asthma, urinary sodium concentration was not. Data from females in this study did not correlate with table salt usage or with urine electrolyte concentration. Unfortunately, this study used only a single sample of urine, and not a 24-hour collection. While a single 24 hour urine collection may not reflect the average daily consumption of salt over several days, it better reflects consumption than does a single sample. This study does not provide solid data either for or against any relationship of salt consumption and asthma severity.

Demissie et al. (1996), surveyed children in Montreal as to asthma symptoms and history, family history, and salt intake (food questionnaire). Spirometry was performed before and after 6 minutes of running in a gymnasium at 90% of age-predicted heart rate. A cross-sectional case-control design was used with 187 cases and 145 controls identified. Both groups were placed in quartiles based on the results of the sale intake score determined from the food questionnaire. A subset of children who had a FEV₁ value greater than 75% of their forced vital capacity underwent methacholine challenge for airway responsiveness. The salt scores did not correlate with asthma (defined as a history of asthma or drop in FEV₁ of greater than 10% postexercise). Salt scores were not correlated with bronchial hyperresponsiveness. However, when comparing the lowest quartile with the highest quartile of salt intake, there was significantly higher airway responsiveness. Unfortunately, the measure of salt intake was crude and unvalidated, leaving little confidence in the determination of salt consumption. Second, the intakes were compared to the presence or absence of asthma, not the severity of asthma. Finally, despite the gross measurements used, there remained an increase in airway responsiveness comparing the low to the high levels of salt intake.

While there are many epidemiologic and cross-sectional studies that contribute support to the possible relationship between dietary salt and severity of asthma, other investigations have not found such an association (Britton et al., 1994; Devereux et al., 1995; Sparrow et al., 1991; Zoia et al., 1995).

**Interventional studies**

The work by Stoesser and Cook (1938) and the earlier epidemiologic and cross-sectional studies (Burney, 1989, 1987a) serve as the foundation for many additional studies using a variety of experimental approaches to determine if dietary salt was associated with the severity of asthma. Javaid and colleagues (1988) performed an interventional study to examine the effect of changing dietary salt intake on bronchial reactivity as determined by a histamine challenge test in 10 individuals with asthma and 5 asthmatics (controls) of both sexes. Baseline 24 hour sodium excretion was 3,588 mg/day in the without asthma, and 2369 mg/d in controls. The dietary salt was then doubled for 4 weeks (4958 mg of sodium per day, with asthma; 4209 mg/d, controls) and the subjects had repeat histamine challenge performed. The high-salt intake significantly increased bronchial reactivity compared to the normal diet in men and women with asthma. Control subjects had normal airway responsiveness on both diets. This study adds support to the concept that elevating dietary salt will worsen airway responsiveness, and that this will occur from a moderate to a high consumption of salt. This study did not find that women failed to alter airway responsiveness to increased dietary salt, and does not support the results of those by Burney et al. (1987a).

Burney and coworkers (1989) followed up on their original observations with an interventional study. They conducted a randomized double-blinded crossover trial comparing sodium supplementation of the normal diet with 1840 mg/d with placebo supplementation in 36 patients with asthma on a low-salt diet (diet details were not reported). Twenty-four hour excretion of sodium was measured. Before the low-salt diet, urinary excretion of sodium was 2438 mg/d. With the low-salt diet and placebo supplements, the excretion was lowered by 736 mg/d in men and by 805 mg/d in women. With the low-salt diet and sodium supplementation, sodium excretion returned to slightly above the initial values. There was a decrease in airway response to histamine challenge in men while on the low-salt diet and taking placebo, as indicated by a significant increase in the dose of histamine required to produce a 10% reduction in FEV₁ (PD₁₀). Subsequently, upon supplementing the low-salt diet with salt to return the dietary levels back to usual, the dose of histamine causing a decrease of 20% in FEV₁ (PD₂₀) was 1.51 doubling-doses lower (i.e., increased airway responsiveness) than when taking placebo (low-salt diet only). This effect was not observed in women with asthma. Thus, in men with asthma, lowering dietary salt intake for 2 weeks reduced their airway hyperresponsiveness. Interestingly, when their low-salt diet was supplemented with salt for 2 weeks, their airway hyperresponsiveness was greater than when they entered the study. The fact that women with asthma did not demonstrate any alteration in their airway hyperresponsiveness by diet or supplements supported their earlier epidemiologic finding (Burney, 1987a). The explanation for this possible gender differential in effect of dietary salt on airway responsiveness in asthma remained to be determined, or why their results differed in this regard from Javid et al. (1988).

Carey et al. (1993) studied 27 men with asthma receiving 5 weeks of 4600 mg of slow sodium release capsules or placebo capsules daily in a random order (double-blinded, crossover design), while ingesting a low-salt diet (1840 mg/d of sodium). Pulmonary function testing and methacholine challenge was performed initially, then at the end of each 5-week period. Twenty-four hour urine excretions documented the salt intakes. Daily peak flows were recorded by
the patients, as was medication use. On the normal diet, sodium excretion was 3657 mg/d. The low-salt diet plus placebo produced a 24-hour excretion of sodium of 2029 mg/d, and, the low-salt diet plus sodium supplement yielded 6716 mg of sodium per day. The low-salt diet plus placebo was compared to the low-salt diet plus sodium and was associated with lower methacholine reactivity, decreased bronchodilator usage and higher peak expiratory flow rates and FEV₁ values. While this study lacks a control, nonasthmatic group, the research design permits drawing a reasonable conclusion that lower salt intakes were associated with improved pulmonary function, reduced asthma symptoms and medication use, and reduced airway hyperresponsiveness. This study only used male subjects, so no conclusion with regard to women with asthma and this type of protocol can be drawn.

Medici et al. (1993) directly addressed the question of dietary salt reduction and supplementation on severity of asthma. Additionally, they examined the possibility that chloride ion is important in this potential effect. Using a crossover design, 14 individuals with asthma (9 men and 5 women) were placed on a low-salt diet (5–6 g/d of salt; 1978–2369 mg of sodium) for 2 weeks. Subjects then consumed nine capsules throughout the day containing 1 g of salt or placebo for 3 weeks. The subjects then crossed over treatments for an additional 3 weeks. Patients then received 3 weeks of sodium citrate as the supplement (in solution to equal the amount of sodium received with salt supplementation). After this period, subjects returned to their usual diet and were followed for 3 weeks. Medication use and peak expiratory flows in the morning, noon, and evening were logged daily. Twenty-four-hour urine collections documented electrolyte consumption, and serum electrolytes documented potential blood changes. Laboratory pulmonary function testing and methacholine challenge were performed at regular intervals throughout the study.

The values for sodium and chloride consumption in this study (Medici et al., 1993) were 1817 mg sodium, 2982 mg chloride on the low-salt diet; 3151 mg sodium, 4651 mg chloride on the high-salt diet; 3083 mg sodium 3160 mg chloride on the sodium citrate diet; and 2530 mg sodium, 3905 mg chloride on the patients’ usual diet. Patients reported worsened asthma symptoms and increased inhaled steroid use on the high salt diet. Resting pulmonary function was also reduced on the high-salt diet. However, changes in dietary salt had no demonstrable effect on airway responsiveness as measured by methacholine challenge. Sodium citrate loading did not alter these outcomes, implicating the sodium ion as an important contributor to these observed effects of salt loading. There was no indication that women responded differently from men. This study lacked a control, nonasthmatic, group, for comparison with the individuals with asthma as to pulmonary function. Additionally, the asthmatics continued on their medications during the study and the medication was adjusted if peak expiratory flow (PEF) declined. Thus, it is difficult to interpret the results as to failure of the dietary changes to affect airway responsiveness, as the medications potentially would be normalizing this response.

Tribe and colleagues (1994) carried out an investigation to study dietary sodium intake and the airway response to methacholine in relation to cellular sodium transport in individuals with asthma (Tribe et al., 1994). Men with (n = 27) and without asthma (n = 25) were tested while on their usual diet. Diet was not altered. Twenty-four–hour urine collections were used for electrolyte excretion values. Methacholine challenge was used to measure airway responsiveness. Blood leukocytes were used as a model for sodium transport mechanisms. Average sodium excretions were 3887 mg/d for individuals with asthma and 3818 mg/d for controls. Regression analysis revealed a significant positive relationship between 24-hour sodium excretion and airway responsiveness. Additionally, the result from the leukocyte study suggested that a serum-borne factor found in asthmatic serum caused increased sodium influx into leukocytes and was related to the degree of hyperresponsiveness. However, this effect was independent of the effect of 24-hour sodium excretion on airway responsiveness. It is of interest that the small range of dietary sodium intakes represented here resulted in altered airway responsiveness. This study would have been enhanced had dietary salt been varied across a wide range to determine the effects on the outcome variables. However, these data do support the concept of a negative impact of dietary salt on airway responsiveness.

Lieberman and Heimer (1992) examined the hypothesis that the amount of daily salt intake influences the severity and lability of asthma as measured by PEF and the difference in PEF during the day. Seventeen (17) individuals with asthmatics (9 men and 8 women, 27–62 years of age) were followed while on their normal diet, after 2 weeks of a low-salt diet, and after 2 weeks of a high-salt diet plus daily salt tablets. PEF was self measured at home three times daily morning, noon, and night, prior to medications. Twenty-four–hour urine collections served as surrogate measures of daily intake. Normal diets resulted in sodium excretion of 3381 mg/d; low-salt diet, 1,932 mg/d; and, high-salt diet, 4623 mg/day. PEF did not change with diet, nor did PEF lability. Gender did not have any influence. Severity of asthma was self-monitored by PEF, and this is generally a reliable technique. While subject numbers were low and there was no control, nonasthmatic, group, these data do not support the general concept of a relationship between sodium intake and asthma severity. However, airway responsiveness was not measured and only resting pulmonary function was determined. While participants were not taking corticosteroids and refrained from inhaler use prior to PEF measurement, 10 subjects were on daily oral theophylline that presumably would improve their PEF values. Therefore, these data cannot be extended to those with active disease.
In a recent Cochrane Database Systematic Review, Arden and Ram (2003) assessed the effect of dietary sodium reduction in patients with asthma. The authors identified 56 relevant abstracts, whereby 15 full-text studies were reviewed. Only 5 studies fulfilled the inclusion criteria of being randomized controlled trials, all of which are also reviewed in detail within this present review (Burney et al., 1989; Carey et al., 1993; Gotshall et al., 2000; Lieberman and Heimer, 1992; Medici et al., 1993). A meta-analysis of selected data from three of these studies (Gotshall et al., 2000; Lieberman and Heimer, 1992; Medici et al., 1993), along with individual study analysis (Burney et al., 1989; Carey et al., 1993) indicated that there was a pattern suggestive of a small improvement of pulmonary function with a salt-restrictive diet and a small reduction in bronchodilator use. Based on the available evidence at the time of the review and considering the small sample size of these studies, along with the possibility of a “type 2” error being committed, the authors decided it was not possible to conclude whether dietary reduction is beneficial as a treatment of asthma. Unfortunately, in every study reviewed and reanalyzed, only resting, baseline, unchallenged pulmonary function data were used. In the review, the study by Medici et al. (1993) was used as the only study with methacholine challenge data. As reviewed above within the present review, this study (Medici et al., 1993) has some design flaws that limit interpretation of these data. So, the conclusion of these reviewers (Arden and Ram, 2003) does not necessarily extend to airway hyperresponsiveness in asthmatics.

The divergent findings of the studies reviewed to this point are due, at least in part, to several factors. Measures or estimates of salt intake varied markedly. Most studies were performed with subjects on their usual salt diet, which is typically high and the range of intakes is very small. Thus, those studies that varied intakes experimentally provide stronger data. Studies often had nonasthmatic populations as the predominate number within the study. Medications, when reported, were not often controlled and may have interfered with the potential results. Resting pulmonary function was often the only measured variable. Individuals with asthma who are either well-controlled medically, or who are not currently experiencing a response to a trigger, often have resting pulmonary function within normal limits.

In summary, the studies presented to this point that have investigated potential relationships between dietary salt intake and severity of asthma or airway hyperresponsiveness have provided only moderate support for this concept. This question requires a randomized, controlled large clinical trial that includes dietary control, well-diagnosed individuals with asthma, a control group without asthma, careful attention to confounders (such as medications and other dietary factors), and that has both direct pulmonary function assessment with pulmonary function at rest and during airway challenge, and has indirect measures such as daily symptoms and medication use.

### DIETARY SALT AND EXERCISE-INDUCED BRONCHOCONSTRICION

Most individuals with chronic asthma demonstrate post-exercise decrements in pulmonary function if challenged with the appropriate exercise intensity. Thus, exercise provides an indirect challenge to airways that provides a safe and easily controlled experimental condition with which to evaluate potential interventions such as dietary components on airway responsiveness. Therefore, exercise has been used in a series of experimental protocols to evaluate modifications in dietary salt intake on the severity of EIB.

The initial studies were conducted by Mickleborough and colleagues (2000, 2001a) and utilized a double-blinded randomized crossover study to assess the effect of dietary salt manipulation on the severity of EIB. Fifteen (15) subjects with solitary EIB (without asthma) entered the study on their normal-salt diet, and then were placed on either a low-salt diet or a high-salt diet for 2 weeks. A 1-week washout period on the normal-salt diet was included before crossing over to the second treatment period of 2 weeks. Pre-exercise and postexercise pulmonary function tests were performed after each treatment period. For all three diet treatments 24-hour–urinary sodium excretions were significantly different (normal-salt diet = 3,630 mg/d; low-salt-diet = 958 mg/d; high-salt diet = 8133 mg/d). Comparing pre-exercise to postexercise changes in pulmonary function measurements, forced vital capacity (FVC) and FEV1 significantly improved by +0.95 L and +0.4 L on the low-salt diet, whereas the high-salt diet induced significant reductions of −0.22 L and −0.37 L in FVC and FEV1, respectively. The data demonstrated for the first time that 2 weeks of dietary salt loading worsened and 2 weeks of salt restriction improved postexercise pulmonary function in solitary EIB subjects. This study did not include a control group without asthma for comparison.

In a follow-up study, Gotshall and coworkers (2000) conducted a double-blinded randomized crossover study to assess the effect of 2 weeks of dietary salt loading and restriction on eight subjects with solitary EIB, but included a group of eight non-EIB (control) subjects. Otherwise, study conditions were identical to the previous study (Mickleborough et al., 2000). Pulmonary function was assessed pre-exercise and postexercise and before and after each treatment period (normal-, low-, and high-salt diet). Diet had no effect on pre-exercise pulmonary function values in either group and had no effect on postexercise pulmonary function values in control subjects. However, the low-salt diet improved and the high-salt diet worsened postexercise pulmonary function values in EIB subjects. FEV1 decreased by 14% ± 6% on the low-salt diet, 20% ± 7% on the normal-salt diet, and 24% ± 6% on the high-salt diet at 15 minutes postexercise. Dietary goals were achieved as urinary sodium excretion decreased significantly on the low-salt diet (1335 mg/d) and increased significantly on the high-salt diet (6750 mg/d).
mg/d). This study confirmed the previous observations (Mickleborough et al., 2000) that a high-salt diet exacerbates and a low-salt diet ameliorates the severity of EIB in those with solitary EIB, while having no effect on pulmonary function in control subjects.

Recently, Gotshall and coworkers (2003) conducted a study to determine whether a shorter regimen of dietary salt restriction would prove as effective as 2 weeks of salt restriction in reducing the severity of EIB. Ten (10) subjects with solitary EIB and 10 control (non-EIB) subjects participated in a randomized double-blinded trial and were placed either on approximately 1500 mg of sodium for 2 weeks, which constituted the low-salt diet or on their normal = salt diet. Pre-exercise and postexercise pulmonary function tests were performed at the end of 1 and 2 weeks. The EIB subjects demonstrated significant reductions in FEV1 of −27 ± 5%, −24% ± 5% and −20%–8% on the normal-salt diet at 1, 5, and 15 minutes postexercise. However, after 1 week on the low-salt diet, postexercise FEV1 Improved significantly to −4.5% ± 4%, −8.9% ± 4% and −7.6% ± 3% and after 2 weeks on the low-salt diet to −3.2% ± 7%, −8.9% ± 10% and −7.7% ± 5% at 1, 5, 15 minutes post-exercise respectively. The low-salt diet markedly reduced the severity of EIB to subclinical levels (less than 10% decrease in postexercise FEV1 compared to pre-exercise values) and had a similar effect at both 1 and 2 weeks.

Because salt comprises both sodium and chloride, it may be that the anion, chloride, plays a significant role in the influence of salt on EIB. In hypertension research, there have been several studies implicating the chloride ion as the main contributor to elevated blood pressure during dietary salt loading (Kurtz et al., 1987; Shore et al., 1988). Sodium loading with anions other than chloride (e.g., sodium citrate and sodium phosphate loading) have failed to produce elevated blood pressures of salt-sensitive hypertension (Kurtz and Morris, 1984; Shore et al. 1988). Medici et al. (1993) attempted to evaluate an independent contribution of the chloride ion on the severity of asthmatic symptoms. Fourteen (14) individuals with asthma were placed on high sodium chloride or sodium citrate diets. Salt loading, regardless of type, worsened resting pulmonary function (e.g., FEV1 and PEF rate) and asthmatic symptoms, and increased the use of inhaled corticosteroids.

Therefore, Mickleborough and colleagues (2001b) evaluated the influence of low and high chloride diets on the severity of EIB. The study design and protocol was conducted in a similar fashion as the study performed by Gotshall et al. (2000) with the only difference being that upon entering the study on the normal-salt diet, all subjects (EIB, n = 8, and control, n = 8) were either placed on a low-salt diet (low sodium, low chloride) for 2 weeks or a sodium bicarbonate (NaHCO3) diet (high sodium, low chloride) for 2 weeks. The data confirmed earlier observations (Gotshall, et al., 2000; 2001a) that low-salt diet significantly blunted the decline in postexercise pulmonary function in solitary EIB subjects without any effect in control subjects. Additionally, the data indicated that dietary chloride reduction coupled with dietary sodium elevation (NaHCO3 loading) also attenuated the decrement in postexercise pulmonary function in EIB subjects, but not to the extent of the low-salt diet (low dietary sodium and chloride). FEV1 decreased 7% ± 5% on the low-salt diet, 14% ± 11% on the NaHCO3 diet, and 19 ± 6% on the normal-salt diet. Urinary excretion of sodium was 1761 ± 571 mg/d, 3477 ± 622 mg/d and 6266 ± 2016 mg/d on the low-salt, normal-salt and NaHCO3 diet, respectively. There was no significant difference in urinary chloride excretion between the low-salt diet (3043 ± 453 mg/d) and NaHCO3 diet (2722 ± 241 mg/d). These data suggest that both the sodium and chloride ion may contribute to the deterioration of the severity of solitary EIB seen after a normal-salt diet or high-salt diet.

In a further attempt to delineate a possible mechanism by which dietary salt loading might exacerbate EIB, Mickleborough and coworkers (Mickleborough et al., 2001c) used the guinea pig model for EIB. The guinea pig manifests dry-gas hyperpnea-induced airway obstruction (HIAO) that parallels the response seen in human subjects with EIB. Because it has been suggested that EIB and HIAO in guinea pigs are mediated by similar mechanisms, the purpose of the study conducted by Mickleborough and colleagues (2001c) was to determine whether altering dietary salt consumption also exacerbated HIAO in guinea pigs. Furthermore, in order to delineate a possible mechanism by which dietary salt may exert an effect on airway responsiveness, the potential pathway of action of dietary salt was investigated by blocking leukotriene (LT) production during HIAO in guinea pigs. Thirty-two (32) guinea pigs were divided into two groups. One group (n = 16) of animals consumed a normal-salt diet (0.75% salt, which is the normal salt content of guinea pig feed) for 2 weeks, whereas the other group of animals (n = 16) ingested a high-salt diet (2% salt). At the end of each treatment period, the animals were anesthetized, cannulated, tracheotomized, and mechanically ventilated during a baseline period and during two dry gas hyperpnea challenges. After the first challenge, masoprocol (nordihydroguaiaretic acid), which is a LT biosynthesis and lipoxygenase inhibitor, was administered. The high-salt diet elicited significantly
higher airway inspiratory pressures (Ptr) than the normal-salt diet postchallenge. However, after infusion of masoprolol and a second hyperpnea challenge, Ptr was significantly reduced in both groups. Nonetheless, the high-salt diet continued to elicit significantly higher Ptr than the normal-salt diet. Urinary leukotriene E4 (LTE4) excretion significantly increased in the high-salt group compared to the normal-salt group. This novel study demonstrated, for the first time, that elevated dietary salt worsened the HIAO response compared to a normal-salt diet. These data suggest that dietary salt may interact with an important inflammatory mediator system, LTs, resulting in enhanced airway response to hyperpnea. The potential interactions of dietary salt and LT production and release in this animal model have yet to be determined.

One interpretation of this study by Mickleborough and coworkers (2001c) suggests that high salt loads may enhance the release of leukotrienes from effector cells in the airways of guinea pigs subjected to dry gas hyperpnea. An alternative explanation is that salt loading may work upstream at the initiating stimulus of EIB and HIAO by altering airway osmolarity, resulting in the subsequent release of inflammatory mediators and bronchial smooth muscle contraction. Inflammatory mediators may cause bronchial smooth muscle to contract either by direct or indirect (e.g., triggering neural responses) actions and cause an increase in vascular permeability and airway mucus secretion, which subsequently cause airway obstruction (Virant, 1992). The effect of salt-induced release of leukotrienes in airways of EIB subjects has not been determined.

In summary, these series of studies have provided strong evidence that lowering salt intake reduces and that elevating salt intake increases the severity of the airway response to the hyperpnea of exercise in those with solitary EIB. While there are large variations in individual responses, a low-salt diet (approximately 1500 mg of sodium per day) reduces the severity of EIA to below the diagnostic limit of a 10% decrease in postexercise FEV1 (Fig. 1). These studies provide no support for the concept that women respond differently than men in this regard. These studies were limited to those individuals without asthma with EIB (solitary EIB). Thus, these data cannot necessarily be extended to those with asthma who have EIB. The data do provide a strong rationale to continue to study this potential relationship and extend the results to those with diagnosed asthma. Furthermore, the underlying mechanism of any such relationship remains to be determined.

**POTENTIAL EFFECTIVE DOSE OF A LOW-SALT DIET TO REDUCE SEVERITY OF ASTHMA**

The low-salt diet in the studies evaluating the effect of dietary salt manipulation on the severity of EIB (Gotshall et al., 2000; Mickleborough et al., 2000, 2001a, 2001b) ranged from 958–1761 mg of sodium per day. This range is two to three times the recommended daily allowance (RDA; National Research Council, 1989), below the 2400 mg per day limit for reducing hypertension (Krauss et al., 2000), and well below the average daily sodium intake of Americans (typically in excess of 3900 mg of sodium per day, which is equivalent to 9.9 g of sodium chloride per day; National Research Council, 1989). Based on these studies (Gotshall et al., 2000; Mickleborough et al., 2000, 2001a, 2001b) a target of less than 2400 mg/d of sodium (or 6 g of salt per day) for reductions in the severity of EIB can be recommended. At present, salt (sodium chloride) intake among adults and children in the United States averages at least 9 g/d, with large numbers of adults consuming 12 g/d, resulting in levels 10–15 times the basal sodium requirement for adults and growing children of 500 mg of sodium per day (Elliott et al., 1996; Elmer et al., 1991). Approximately 15% of the current salt intake comes from salt added in cooking and at the table, while 10% comes from the natural content of foods. The remaining 75% of all salt eaten comes from salt added in processing and manufacturing of foods (Elmer et al., 1991). A variety of studies have indicated that low-salt diet is both feasible and acceptable to patients because of the successful marketing of no-salt or low-salt products. No negative consequences of these low-salt diet interventions have been observed, and in some cases improvement in the intake of other nutrients has occurred.

**FIG. 1.** Composite data to demonstrate relative influence of varying dietary salt on pulmonary function in exercise-induced bronchoconstriction (EIB). A decrease in postexercise forced expiratory volume in 1 second (FEV1) of 10% is the threshold for EIB. NSD, normal-salt diet; LSD, low-salt diet; HSD, high-salt diet; NaHCO3, sodium bicarbonate diet. (Data compiled from references: Gotshall et al., 2000; and Mickleborough et al., 2001b).
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