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## Clinical Nutrition and Metabolism Group Symposium on ‘Nutrition and lung health’

### Nutrition and lung health

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There is an increasing interest in the relationship between nutrition and lung health. Epidemiological studies suggest that dietary habits may have an influence on lung function and the tendency to common lung diseases such as asthma, chronic obstructive pulmonary disease (COPD) and lung cancer. In particular, a diet rich in fresh fruit and fish has been associated with a salutary effect on lung health. End-stage COPD is associated with a state of nutritional depletion which is refractory to conventional nutritional supplementation. In contrast, malnutrition associated with cystic fibrosis is amenable to nutritional therapy, which has been shown to improve prognosis in this disease.

#### Chronic obstructive pulmonary disease: Lung cancer: Cystic fibrosis: Nutritional therapy

Factors related to nutrition are implicated in the pathogenesis of a wide variety of diseases. Most attention has focused on the now well-established link between diet, energy imbalance (obesity) and cardiovascular disease, particularly coronary artery disease (World Health Organization Expert Committee, 1982). The critical role of nutrition has been recognized also with regard to chronic disease states of the other organ systems, e.g. the primacy of dietary measures in the management of metabolic disorders such as diabetes (Lean *et al.* 1991), the relationship between poor nutritional status and failure of the immune system (Chandra, 1990), the value of nutritional support and dietary modification in renal and liver failure (Lee, 1980), and the importance of special diets in the management of disorders of the gastrointestinal system (Cummings, 1993). The part played by nutrition in the pathogenesis of cancer has also been the subject of extensive research (Doll & Peto, 1981).

In striking contrast to the situation pertaining to the other organ systems, the relationship between nutrition and diseases of the lung and respiratory system has received little attention. Major texts of nutrition often mention the lungs only in passing, or not at all (Garrow & James, 1993). However, this relative neglect is easily explained. First, the three most common lung diseases (asthma, chronic obstructive pulmonary disease (COPD; a term used to describe chronic bronchitis and emphysema) and lung cancer) have a fairly well established aetiology. In the case

of asthma, genetic factors and exposure to allergens have been identified as playing a key role, whilst COPD and lung cancer are largely the result of cigarette smoking (Doll & Peto, 1976). The influence of genetic factors and atopy on asthma, and cigarette smoking on COPD and lung cancer is so strong and ‘obvious’ that other factors such as nutrition have been subjected to less scrutiny than would otherwise have been the case. Second, even in those respiratory diseases like cystic fibrosis, where nutrition plays a significant role in the manifestations and management of the disease, the relationship between nutrition and disease state is not directly causal, rendering study of the role of nutrition less attractive. However, interesting new evidence which has emerged over the past decade suggests that there might be a significant link between dietary intake of certain nutrients and lung health (Sridhar, 1995a). In particular, epidemiological studies point to an association between decreased risk of chronic lung disease and a high intake of foods rich in antioxidant activity (Shahar *et al.* 1994). These studies suggest that not only do high intakes of fresh fruits, vegetables and certain fish oils appear to offer protection against lung disease, but also that these food items seem to have a clear, if mild, salutary effect on lung function. At the same time, studies attempting to obtain insight into the molecular and chemical basis of lung disease have, using techniques of molecular biology, identified oxidant–antioxidant imbalances as the basis of lung tissue damage in

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 s; FFM, fat-free mass.

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these illnesses (Kondo *et al.* 1994), lending a biological plausibility to the conclusions of the epidemiological studies.

Also receiving increasing attention is the other side of the relationship between nutrition and lung disease, the deleterious effect of lung disease on a patient's nutritional status ('the pulmonary cachexia syndrome') and the adverse prognostic implication of this nutritionally-depleted state. Patients with lung disease who begin to lose weight have a greater mortality and morbidity from their disease than their weight-stable peers (Rogers *et al.* 1992). Whilst the mechanisms that result in weight loss in severe lung disease remain poorly defined (Sridhar, 1995b), the profound implications of nutritional depletion have prompted a renewed interest in the subject.

The aim of the present review is to summarize the information currently available on the links between nutrition and lung health, addressing both aspects of this interesting relationship: the effect of nutrition (and dietary habits) on lung health and disease; the effect of lung disease on nutritional status. The present paper is broadly divided into two sections: the first, dealing with the impact of malnutrition and deficiency of specific nutrients on lung function and disease; the second, describing the nutritional consequences of lung disease. The articles following the present overview focus on more specific aspects of the link between nutrition and lung health: the links between diet and asthma and COPD (Smit *et al.* 1999), the mechanisms and management of the pulmonary cachexia syndrome (Congleton, 1999), and diet and lung cancer (Virtamo, 1999).

### Malnutrition as a cause of lung disease

#### *The effects of starvation on lung function*

In 1919 Benedict *et al.* (1919) published the results of their starvation experiments on human volunteers. Various physiological changes which accompanied the weight loss (about 10% of initial body weight) on this diet were measured. After weight loss the overall basal heat production or, as it is now known, resting energy expenditure, fell by 20% and O<sub>2</sub> consumption by 18%. Minute ventilation (the total volume of air breathed in 1 min) was recorded to have fallen from an average of 5.09 litres/min to 4.49 litres/min. The negative effect of nutritional deprivation on ventilatory function was confirmed by the Minnesota experiments (Keys *et al.* 1950). Vital capacity (the maximum amount of air expired by a subject after a maximal inspiration) fell by an average of 390 ml, while minute ventilation fell from an average of 4.82 litres to 3.35 litres. Most interestingly, respiratory efficiency, which was arbitrarily defined as the amount of O<sub>2</sub> removed (in ml) per litre expired air, decreased by 16% during aerobic work and 11% during anaerobic work. While the vital capacity returned to baseline values after 12 weeks of refeeding, measures of respiratory efficiency took longer (20 weeks) to return to normal. Although no measure of respiratory muscle strength was made, the conclusion was that the deleterious effect of starvation on ventilation resulted from weakness of the respiratory muscles.

The most striking observations on the effect of starvation on respiratory morbidity come from the studies by the Jewish physicians in the Warsaw ghettos (Winick, 1979). Under the leadership of Dr Israel Milejowski, a group of investigators studied and described in remarkable detail the clinical and pathological consequences of food deprivation. It was noted that in severe malnutrition, minute ventilation decreased to half normal values and there was an increased tendency to pulmonary infection, including tuberculosis ('death from starvation is death from pneumonia'). Most interestingly, starvation was described as causing a condition of 'atony of the lungs' which was described thus: 'However, in the few cases where X-rays were available we could demonstrate radiolucency of the lungs, free costophrenic angles, lowering of the lower lung borders, and decreased pulmonary mobility in the absence of tubercular signs. This new syndrome of atony of the lungs, never described before in hunger disease, was characteristic and consistent in the lungs of our patients'. These features would now be readily recognized as characteristic signs of emphysema. Stein & Fenigstein (1946), who carried out the autopsies, reported that findings of emphysema were present in fifty of the 370 cases. In twenty-six of those cases the individuals were less than 40 years of age, and the authors drew particular attention to the singular appearance of 'senile emphysema' in this young population. Even allowing for the fact that the authors did not define precisely their criteria for making a diagnosis of emphysema, these remarkable observations were the first to describe in any detail the link between nutritional depletion and emphysema, a subject which was to command the attention of investigators once again almost half a century later (see Wilson *et al.* 1985).

#### *Dietary habits, lung function and chronic obstructive pulmonary disease*

Whilst studies earlier this century were of the effects of starvation on global lung function, more recent studies have focused on the association between lung health and dietary intake of specific food substances and nutrients. Analysis of data from a representative sample of adults in the USA, examined as part of the Second National Health and Nutrition Examination Survey, suggested that higher dietary intake and serum concentrations of vitamin C had a protective effect against respiratory symptoms (Schwartz & Weiss, 1990). Independent of cigarette smoking, there was an inverse relationship between bronchitis and dietary vitamin C intake. Strachan *et al.* (1991) in a study of 1502 non-smokers and 1357 smokers with no history of respiratory disease found that fresh fruit consumption in winter, and by implication habitual fruit consumption, was significantly related to ventilatory function not only in current smokers but also lifelong non-smokers. After adjustment for differences in anthropometric measures, socio-economic status and smoking habits, the forced expiratory volume in 1 s (FEV<sub>1</sub>) of the group with a 'low' intake of fruit was less than that of the 'high' intake group by about 80 ml. A cross-sectional study of over 2500 adults in Nottinghamshire (Britton *et al.* 1993) revealed that not

only was FEV<sub>1</sub> directly related to habitual vitamin C intake (after adjustment for smoking habits), but also that the effect of vitamin C on FEV<sub>1</sub> was greater in the older age-group, suggesting that vitamin C had a protective effect on lung function. Analysis of the data collected for the First National Health and Nutrition Examination Survey has lent more support to this view (Schwarz & Weiss, 1994), as have studies in children (Cook *et al.* 1997). More recently, a group of Dutch investigators (Grievink *et al.* 1998) have documented an association between a high intake of vitamin C or  $\beta$ -carotene and better lung function. In addition to these cross-sectional studies, in a longitudinal study, another group of Dutch investigators (Miedema *et al.* 1993) examined the relationship between diet and the incidence of chronic non-specific lung disease (a collective term embracing the diseases of asthma, bronchitis and emphysema) over a 25-year period, and found that after adjustment for confounding factors, fruit intake was inversely related to the incidence of lung disease. The other dietary components that have received attention as a protector against tendency to smoking-induced lung disease are the *n*-3 polyunsaturated fatty acids (Shahar *et al.* 1994; Britton, 1995).

In summary, whilst not showing causation, all these studies appear to show a consistent pattern, associating better lung function and relative freedom from chronic lung disease with intake of nutrients high in antioxidant (fresh fruit) and anti-inflammatory (fish oils) activity. What is particularly interesting about the results of these community-based studies is that, in theory, they fit quite well with the evidence that techniques of molecular biology are beginning to uncover about the pathogenesis of obstructive lung disease. It seems most likely that tissue damage in COPD is an inflammatory phenomenon related to oxidant-mediated damage (Heffner & Repine, 1989). Although antioxidant enzyme activity is increased in alveolar macrophages of young asymptomatic smokers (Hoidal *et al.* 1981), similar cells from elderly current smokers show decreased antioxidant enzyme activity, and profound oxidant-antioxidant imbalance (Kondo *et al.* 1994). It appears therefore that lung damage leading to obstructive lung disease results from unopposed oxidant activity. The finding that fresh fruit and fish oils, with their high antioxidant and anti-inflammatory activity, offer protection against such damage is thus in keeping with the currently postulated mechanisms.

#### *Nutrition: the missing link?*

It is well known that although most patients with COPD are smokers, only a minority of smokers proceed to develop severe lung disease, suggesting that amongst smokers there are wide variations in the tendency to develop COPD (Pride, 1990). Some epidemiological studies have suggested that there are factors related to social class, but unrelated to smoking, that may determine susceptibility to lung disease (Burr & Holliday, 1987). Studies have also shown measures of lung function (FEV<sub>1</sub> in particular), independent of smoking, to be predictors of all-cause mortality (Hole *et al.* 1996). On the basis of the foregoing studies, it is tempting to speculate that the differing tendencies to develop lung

disease and the predictive value of lung function are in some way related to dietary habits and habitual antioxidant vitamin consumption.

#### *Clinical implications*

If this is the case, is there a diet that can protect against obstructive lung disease? Should patients at risk of developing COPD, i.e. smokers, be advised to take supplements of antioxidant vitamins? Association does not imply causation, and all the studies cited suggest no more than an association. Although most of these studies have taken care to avoid vitiation of results by well-recognized confounding factors (age, smoking, energy intake, socio-economic status), it is still possible that there are other factors, including genetic ones, that may have a bearing on susceptibility to lung disease. There is as yet no evidence which bridges the gulf between the community-based studies and laboratory-based studies to show that decreased habitual consumption of antioxidant vitamins is accompanied by failure of antioxidant defence mechanisms in the lung. Furthermore, more importantly, antioxidants given as supplements may not have the same effect as antioxidants obtained from natural sources, and indeed, as in other situations, the use of antioxidant vitamin supplements may be associated with harmful side effects (The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group, 1994).

#### *Dietary influences on asthma*

Asthma is the commonest respiratory disorder affecting the general population. Whilst genetic influences and tendency to atopy have long been recognized as significant influences on developing the disease, dietary influences have also been proposed, particularly to explain the well-documented increase in the disease. Earlier studies appeared to suggest a role for Na intake, with demonstration of a relationship between the response of the airways to histamine and Na intake (Burney *et al.* 1986), and a correlation between increasing mortality from asthma in males and table salt (NaCl) purchases in the community (Burney, 1987). More recent studies have cast some doubt on this hypothesis (Devereux *et al.* 1995), but other dietary elements, including Mg (Britton *et al.* 1994) and Se (Flatt *et al.* 1990), have been postulated as having a role to play in the aetiology of asthma.

#### *Diet and lung cancer*

Epidemiological studies suggest that a high intake of carotenoid-rich vegetables and fruits is associated with a lower risk of cancer, particularly lung cancer (Doll & Peto, 1981). However, studies which have assessed the role of supplementation with specific agents considered responsible for this protective effect ( $\alpha$ -tocopherol and  $\beta$ -carotene) have shown that not only are these vitamin supplements not protective against lung cancer, but also that dietary supplementation may, paradoxically, increase the risk of cancer (The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group, 1994).

### *Respiratory consequences of obesity*

Breathlessness is a common complaint amongst the obese. In addition to global impairment of lung function the obese also suffer from a more specific disorder of breathing during sleep. Obstructive sleep apnoea is a disease characterized by snoring, intermittent cessation of breathing due to upper airway obstruction during sleep, and daytime somnolence. Whilst the disease does occur in a minority of non-obese individuals, it is predominantly a problem of the obese (Douglas & Polo, 1994).

### **Lung disease as a cause of malnutrition**

The fact that weight loss heralded a state of terminal decline in patients with chronic airways disease was known even in the late 19th century (Fowler & Goodlee, 1898). Although the association between weight loss and mortality from lung disease was thus recognized, it was not until the 1960s that attempts were made to investigate this relationship. A number of studies of this period, especially longitudinal studies aimed at predicting the prognosis of patients with chronic airways disease, clearly demonstrated that a significant proportion of these patients suffered from malnutrition. Not only did these studies show that the group that lost weight exhibited a more rapid decline in lung function and exercise tolerance, but they were also more likely to die from their illness in comparison with their weight-stable counterparts. Not much interest was evinced towards the link between malnutrition and lung disease until the last decade, when workers, mainly in the USA, pointed out once more the high prevalence and significant clinical importance of malnutrition in patients with COPD. In contrast to the investigations of the 1960s, the studies of the 1980s and 1990s that have followed the observations of these workers have largely been preoccupied with the clinical rather than the pathophysiological significance of nutritional depletion. Hunter *et al.* (1981) measured nutritional status, dietary intake and immunological responses in thirty-eight patients with COPD, and found twenty-seven showed evidence of weight loss, although their mean recommended intakes for nine vital nutrients (and by implication their overall diet) were above the recommended daily allowances. Skinfold measurements revealed a depletion of both lean body mass and fat stores, although visceral protein stores, as estimated by serum albumin and transferrin, were normal. Nine of the thirty-two patients who underwent immunological testing (intradermal injections of purified protein derivative and *Candida* antigens) showed anergy. Hunter *et al.* (1981) concluded that malnutrition of the marasmic type was widely prevalent in patients with COPD. Subsequent studies have confirmed the prevalence of malnutrition in COPD patients, including some studies examining the incidence of malnutrition in an outpatient population in order to avoid the confounding effect of acute illnesses that hospitalized COPD patients may exhibit. Wilson *et al.* (1985), in an extensive review of the link between nutrition and chronic lung disease, summarized these studies and various other studies and concluded 'malnutrition is a common problem in patients with COPD, so that nutritional assessment, including

anthropometric measures as well as inspiratory and expiratory pressures, should be included in the evaluation of patients with suspected nutritional impairment'.

A more recent study further highlights the problem of nutritional depletion in COPD patients (Wouters & Schols, 1993). These investigators assessed the body composition of a group of 255 patients with moderate COPD (mean FEV<sub>1</sub> 35% predicted value) who were part of a pulmonary rehabilitation programme. Arguing that body weight is not a sensitive measure of nutritional status or body composition, they estimated fat-free mass (FFM) in these patients using the bioimpedance technique. Classification of patients on the basis of body weight and FFM revealed that not only did underweight patients show evidence of depletion of FFM, but that a significant proportion of normal-body-weight patients too were depleted of FFM. These normal-weight patients with low FFM exhibited greater physical impairment than underweight patients with preserved FFM. It appears from this recent and important study that malnutrition may be more widespread a problem than hitherto believed.

### *Pathogenesis of malnutrition in patients with chronic obstructive pulmonary disease*

Although malnutrition has been recognized as a significant problem in patients with COPD, attempts to elucidate the underlying pathophysiology of this phenomenon have been few. Decreased dietary intake (Vandenberg *et al.* 1967), increased energy expenditure consequent upon an increased energy cost of breathing (Donahoe *et al.* 1989), infections (Bates, 1973), tissue hypoxia (Sridhar, 1995b) and drug therapy (Amoroso *et al.* 1993) have all been proposed as being responsible for the state of negative energy balance. It is quite likely that these mechanisms are not mutually exclusive and, to a degree, all of them contribute to weight loss in patients with end-stage lung disease.

### *Nutritional therapy for chronic obstructive pulmonary disease*

The logical consequence of the identification of malnutrition as an adverse prognostic factor in severe COPD has been an attempt to improve prognosis by nutritional repletion. However, in the main, studies of supplementary feeding in this situation have been rather disappointing. Weight gain and improvement in lung function have been achieved at a considerable financial cost (Rogers *et al.* 1992) or, anecdotally, with the addition of anabolic agents such as clenbuterol with an undetermined long-term safety profile (Sridhar *et al.* 1997). Simple supplementary feeding in a routine clinical setting has been shown to be of no value in influencing nutritional status or lung function favourably (Sridhar *et al.* 1994), a situation quite in contrast to the other lung disease associated with malnutrition, cystic fibrosis.

### *Nutrition in cystic fibrosis*

The one disease amongst lung disorders that has been an exception to the rule of relative neglect from nutrition experts is cystic fibrosis (Ramsey *et al.* 1992). Cystic

fibrosis is an autosomal recessive disease of exocrine glands that mainly affects the pancreas and the lungs. Malnutrition is a well-recognized feature of cystic fibrosis, and is the result not primarily of the lung pathology, but of the pancreatic abnormality associated with the disease that leads to malabsorption. Although prognosis in cystic fibrosis is related to pulmonary function, poor nutritional status is an independent predictor of poor outcomes (Kraemer *et al.* 1978). Unlike the situation pertaining to COPD, nutritional therapy, including judicious use of parenteral nutrition, has been shown to have a favourable impact on mortality and morbidity from the disease (Corey *et al.* 1988).

### Conclusions

There is an increasing interest in the relationship between nutrition and lung health.

- (1) Dietary habits and nutritional status appear to have an influence on lung function and the tendency to common lung diseases such as asthma, COPD and lung cancer. The exact nature of the nutrients involved, the magnitude of their influence and the practical implications of these influences remain unclear.
- (2) End-stage lung disease, in particular emphysema, is associated with weight loss and nutritional depletion. Patients with emphysema who begin to lose weight suffer a greater mortality and morbidity from their disease. Standard nutritional supplementation in these circumstances has not been shown to alter outcome.
- (3) In contrast, nutritional therapy has a key role to play in the management of cystic fibrosis. Appropriate nutritional support is associated with decreased mortality and morbidity from the disease.

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