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IMPACT OF NUTRITIONAL SUPPORT ON CHANGES IN FUNCTIONAL STATUS DURING AN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Abstract

Despite the acknowledged importance of nutritional support for COPD patients, it is difficult to accomplish in acutely stressed individuals. A randomized trial of nutritional supplementation during an acute exacerbation was carried out in 16 hospitalized patients for a 2 week period. Six control patients consumed a standard diet supplying 1,951 ± 130 (mean±SEM) kcal and 80 ± 6 g protein/d, while ten treatment patients, in addition to the usual diet received oral supplements (Ensure) or snacks, resulting in an intake of 2,516 ± 129 kcal (p=0.012) and 99 ± 6 g protein/d (p= 0.059). Although the treatment subjects improved their intake over the control group, no significant improvement in nutritional status occurred in either group.

Forced vital capacity (FVC % predicted) improved significantly over the study period in treated vs control subjects (+11.10 ± 4.63 vs -4.50 ± 2.14; p=0.026). No significant changes in forced expiratory volume in one second (FEV_1 % predicted), respiratory and peripheral muscle strength, general well-being scores and dyspnea scores were observed. Nitrogen balances were calculated for 9 subjects, and all were in negative balance (-8.42 ± 1.74 g nitrogen/d) with no difference between groups.

Because of the high doses of methylprednisolone administered (69.6 ± 8.3 mg/d), and their known catabolic effects, we examined whether the dose affected nitrogen balance and muscle strength. Both nitrogen balance (r= -0.73; p=0.025) and grip strength (r= -0.76; p<0.001) worsened with higher doses of steroids. The catabolic process may have resulted from elevated energy requirements, inadequate intake of protein and energy or been induced by high doses of steroids.

Hospitalized COPD patients are highly stressed and catabolic, and the means to preventing protein wasting during an acute exacerbation of their disease remains to be established.

Supported by the FRSQ and APQ.

Résumé

Malgré l'importance reconnue du soutien nutritionnel aux malades attteints de MPOC, il est difficile à réaliser chez les individus en situation de stress aigü. Une étude randomisée de suppléments nutritifs administrés au cours d'un épisode d'exacerbation aigüe a été effectuée sur 16 patients hospitalisés pour une période de deux semaines. Six patients témoins ont consommé un régime alimentaire standard leur donnant 1,951 ± 130 (± SEM moyenne) kcal dont 80 ± 6 g de protéines par jour alors que dix sujets recevaient, outre le régime habituel, des supléments oraux (Ensure) ou des friandises, résultant en une absorption de 2,516 ± 129 kcal (p=0.012) dont 99 ± 6 g de protéines par jour (p=0.059). Bien que les sujets en traitement aient amélioré leur absorption calorique par rapport au groupe témoin, on n'a observé aucune amélioration significative du statut nutritionnel ni de l'un ni de l'autre groupe. Sur la période d'étude, la capacité vitale forcée (CVF % prédite) s'est améliorée de manière significative chez les sujets traités en comparaison avec les témoins (+ 11.1 ± 4.63 par rapport à -4.5 ± 2.14; p=0.026). Aucun changement significatif n'a pu être observé ni dans le volume d'expiration forcée en une seconde (VEF_1 % prédit), ni dans la force musculaire respiratoire et périphérique, ni dans les notes de bien-être général ou celles de dypsnée.

Les équilibres azotés ont été calculés pour 9 des sujets et on a obtenu un équilibre négatif chez tous (- 8.42 ± 1.74 g d'azote par jour), sans différence entre groupes.

En raison des hautes doses de methylprednisolone administré (69.6 ± 8.3 mg/jour) et de leurs notoires effets cataboliques, nous avons voulu déterminer si elles affectaient l'équilibre azoté et la force musculaire. Equilibre azoté (r= -0.73; p=0.025) et force de préhension (r= -0.76; p<0.001) ont tous deux empiré avec des doses plus élevées de stéroïdes. Le processus catabolique peut avoir été le résultat de besoins énergétiques accrus, d'une absorption insuffisante d'énergie et de protéines ou avoir été induit par la posologie élevée de stéroïdes.

Les patients hospitalisés pour obstruction pulmonaire chronique sont cataboliques et sous un stress intense et les moyens de prévenir le dépérissement protéinique durant la phase d'exacerbations aigüe de leur maladie restent à découvrir.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity, hospitalization, and mortality worldwide. In Canada, respiratory diseases are the third leading cause of death for both men and women of all ages.

COPD interferes with the normal function of the respiratory system, and depending on the severity of the disease can severely curtail activities of daily living. COPD patients often lose weight and depending on the population studied and the indicator used to determine malnutrition, between 19 and 60% of patients are classified as malnourished (Hunter et al, 1981, Openbrier et al, 1983, Gray-Donald et al, 1989, Sahebjami, 1993, Laaban et al, 1993, Schols et al, 1989, 1991). The clinical deterioration and diminished life expectancy (Fernandez et al, 1993) that is associated with weight loss has been acknowledged for many years (Wilson et al, 1989). The reasons for the weight loss are not fully understood. The importance of nutritional support for COPD patients is accepted and under well controlled conditions refeeding trials in stable, malnourished COPD patients have been successful in improving the nutritional status and respiratory muscle strength (Wilson et al, 196, Whittaker et al, 1990, Rogers et al, 1992). Attempts at refeeding stable malnourished COPD patients in the community have had mixed results (Knowles et al, 1988, Lewis et al, 1987, Efthimiou et al, 1988 Sridhar et al, 1994, Otte et al, 1989). Many COPD patients are frequently admitted to hospital experiencing extreme shortness of breath, coughing and wheezing. Our study addresses the question of whether hospitalized patients will benefit from nutritional support during an acute exacerbation of their disease.

The text that follows is divided into two parts. The first part, a literature review, begins with a definition of COPD, and a summary of studies of the prevalence of malnutrition among COPD patients. It is followed by a literature review of the effects that protein energy malnutrition has on the clinical course and on the health and well-being of patients with COPD. The review will also look at the proposed causes of weight loss, and the nutritional intervention studies carried out in stable, malnourished COPD patients. Because of the known catabolic effects of glucocorticosteroids, their effect on nutritional status in a variety of diseases will also be examined. The literature review will conclude with an assessment of the nitrogen balance technique, a commonly used tool to evaluate the effectiveness of nutritional therapy and/or measure a patient's catabolic state. The second part includes the rationale of the study, the hypothesis, objective, methods used, results, discussion and conclusion.

PART ONE LITERATURE REVIEW

1.1 Definition

Chronic obstructive pulmonary disease (COPD) refers to a group of pathologic conditions affecting lung parenchyma, intrathoracic airways, or both, causing chronic airflow limitation (Cherniack, 1991). The structural and functional abnormalities lead to the symptoms of cough, sputum production, dyspnea, and impaired gas exchange to varying degrees in different subjects (Desforges, 1993). Although the definition of COPD in its broadest sense includes asthma, bronchiectasis and miscellaneous causes of airflow limitation, the conditions considered in this thesis are limited to emphysema which affects

the lung parenchyma, and chronic bronchitis which affects the airways. A daily cough, productive of sputum for at least 3 months of the year for two consecutive years has to be present before a diagnosis of chronic bronchitis is made, and reflects mucus hypersecretion. Emphysema on the other hand is defined as the destruction of the gas-exchanging parenchyma distal to the terminal bronchioles, leading to the collapse of the abnormally enlarged airspaces and interfering with the transfer of O_2 and CO_2 between the blood and the alveolar air (Hubmayr, 1991). Both components are usually present to some extent in affected subjects.

Although cigarette smoking has been implicated as a major environmental risk factor associated with COPD, exposure to occupational dust and pollution is also thought to be an important cause of COPD (Oxman et al, 1993). The disease may remain asymptomatic for many years and a diagnosis of COPD, using spirometry, is usually made at an advanced stage, when dyspnea is severe enough to interfere with usual activities of daily living and a major loss in lung function has occurred. Carefully planned treatments which include cessation of smoking, bronchodilators, glucocorticosteroids, and respiratory muscle training, will help alleviate some of the symptoms but will not reverse the condition.

1.2 Nutritional status of patients with COPD

It is generally acknowledged that poor nutritional status will contribute to the decline of any disease. It is therefore not surprising that interest in the nutritional status of patients with COPD has resulted in a substantial body of literature indicating many patients are malnourished and at risk of complications.

1.2.1 Criteria used to assess the nutritional status of patients with COPD

The most widely used parameter for assessing the overall nutritional status is ideal body weight (IBW). The Metropolitan Life Insurance height and weight tables are often used as a standard. These tables are based on measurements from policy holders aged 25 - 59, and weight is related to 3 frame sizes, small, medium, and large, based on elbow breadth (Gibson, 1990). Frame size is seldom measured in studies, and the midpoint of a medium frame for a given height is used to determine the ideal weight of a subject. The actual measured body weight is then compared with the ideal weight and the ratio is used to determine the nutritional status (Hunter et al, 1981, Openbrier et al, 1983, Wilson et al, 1989). An IBW of less than 90% is an indication of malnutrition, whereas an IBW between 90 - 120% is considered normal, and an IBW greater than 120% is regarded as overweight.

In addition, a multiparameter nutritional index, that takes into account anthropometric and/or biochemical variables, has also been used by some investigators to define malnutrition (Schols et al, 1989, Laaban et al, 1993). More recent studies suggest the use of the bioelectrical impedance method, the body mass index (BMI), and the deuterium dilution technique for the assessment of nutritional status of COPD patients (Schols et al, 1991, 1993, Sahebjami, 1993). No consensus regarding the definition of malnutrition using these methods has been established, making comparisons between studies difficult. A summary of studies determining the nutritional status of COPD patients is compiled in table 1.

Four studies in the eighties (Hunter et al, 1981, Openbrier et al, 1983, Wilson et al, 1989,

Gray-Donald, 1989) used less than 90% IBW to indicate malnutrition. These investigators found between 24 and 50% of their study population to be malnourished. Subjects were included if they had a diagnosis of COPD, a forced expiratory volume in one second (FEV_1) of less than 70% predicted or were distinctly identified with emphysema or chronic bronchitis. Some subjects were identified from a review of pulmonary function tests (Openbrier et al, 1983), while others (Wilson, 1989) recruited subjects with a diagnosis of COPD (not asthma) and participating in a clinical trial of intermittent positive-pressure breathing. Hunter (1981) selected hospitalized patients one week after admission. Gray-Donald (1989) recruited subjects participating in a trial of negative-pressure ventilation, whose forced expiratory volume in 1 second was less than or equal to, 50% predicted.

Three other studies in the late eighties and early nineties used percent IBW, body mass index (BMI) [kg/height(m^2)] and/or a nutritional index to classify compromised patients. In 1989, Schols studied 153 subjects, and a nutritional index comprising measures of albumin, prealbumin, total lung capacity and percent IBW was used to indicate the presence or absence of malnutrition. Twenty-nine of the 153 participants (19%) were considered malnourished. Laaban et al in 1993, used a nutritional index based on percent IBW, triceps skinfold, midarm muscle circumference, creatinine height index, albumin and prealbumin or retinol binding protein to classify 50 subjects admitted to hospital with acute respiratory failure. Malnutrition was observed in 30 of the 50 subjects (60%). This high number of malnourished subjects included 13 subjects whose body weights were ≥90% IBW but whose nutritional index scores classified them as being malnourished.

Sahebjami in 1993, divided 126 subjects into groups based on body mass index, and found 29 of the 126 (23%) to be underweight with a body mass index of less than 20; 67 subjects (53.2%) were of normal weight, having a body mass index between 20-27, and 30 subjects (23.8%) were overweight with a body mass index greater than 27. In a more recent study (Schols et al, 1993), the prevalence of body mass depletion was determined in 251 clinically stable COPD subjects. Bioelectrical impedance measurements, creatinine height index, and midarm muscle circumference were used to establish depletion of fat free mass. Patients were divided into four groups. Groups I and II consisted of subjects whose percent IBW was below 90%, while subjects in groups III and IV had weights equal or greater than 90% IBW. A further stratification was made based on fat-free mass, measured by bioelectrical impedance method. Fat-free mass was expressed as a percentage of IBW, and females having less than 63% and males having less than 67% fat-free mass were placed in groups I and III respectively, whereas those having a fat-free mass equal to or greater than 63/67% were included in groups II and IV respectively. According to this classification, 138 of the 251 (55%) participants had both a normal weight and fat free mass. Sixty-six (26%) participants had reduced bodyweight and depleted fat free mass, while 23 (9%) of the subjects had reduced body weight but fat free mass was considered normal. However, 24 subjects whose body weights were equal to, or greater than, 90% IBW had depleted fat free mass, suggesting that normal weight individuals are not necessarily well nourished, corroborating findings by Laaban (1993). A substantial number of subjects were taking maintenance glucocorticosteroids, and as will be described in greater detail in section 1.6.1, the catabolic effects of the

glucocorticosteroids are not immediately evident when body weight alone is used as an indicator of nutritional status.

The results in table 1 suggest that the number of malnourished COPD patients varies substantially across studies. Some clarification is necessary. The numbers reported by Hunter (1981) are somewhat misleading. There was no significant difference between patients' actual weight and ideal body weight, whereas their actual body weights were significantly different ($p<0.001$) from their usual weight. Using the criteria of %IBW as an indication of malnutrition, most subjects would not have been considered malnourished. However, 27 of the subjects showed an involuntary weight loss between 1 and 21% of their usual weight over the previous year. Weight loss per se is a distressing signal indicative of some catabolic event, and should alert clinicians to investigate these individuals further. The 60% reported to be malnourished by Laaban (1993) is much higher than other studies, and the poor nutritional status is thought to have been the result of long-standing malnutrition. This study raises an important problem. Thirteen subjects whose IBW was ≥90% were included in this category based on low measurements of triceps skinfold, midarm muscle circumference and some biochemical indices. Weight alone will not identify all compromised individuals, in particular COPD patients with acute respiratory failure (Laaban, 1993) often show marked expansion of body water masking malnutrition. Openbrier (1983) used only subjects with emphysema and they and others (Wilson, 1985) have observed a generally poorer nutritional status among patients with emphysema.

Bioelectrical impedance method estimates the proportion of metabolically active fat free

mass in the body, and depends on the conduction of a low voltage current through electrolyte-containing fluids of the body. Whole body resistance is used to measure fat-free mass (Schols et al, 1991). Bioelectrical impedance has been shown to be a safe, convenient, and feasible alternative in the evaluation and monitoring of nutritional status in normal and critically ill subjects (Lukaski et al, 1985, Robert et al, 1993). The usefulness of this method in COPD patients has not been established, since it has only recently been used in this population (Schols et al, 1991, 1993). Edema, ascites, over-hydration, dehydration will change resistance measurements and may invalidate the method (Gibson, 1990).

One study (Schols et al, 1991) validated the use of bioelectrical impedance in 24 men and 8 women with severe but stable COPD, using deuterium dilution as a reference method. Fat-free mass obtained from bioelectrical impedance was compared with fat free mass measured by deuterium dilution and a high correlation ($r=0.93$, $p<0.001$) was found. Deuterium dilution estimates total body water, which in turn reflects the active tissue mass, and using standard equations fat-free mass can be calculated (Lukaski, 1985). Total body water and the subsequently calculated fat-free mass relies on a constant hydration factor which in the elderly, the acutely ill, the thin or obese, may be different (Kehayia, 1993). Although the doubly labelled water method has been used in healthy elderly men and women for the determination of energy expenditure (Pannemans, 1993, Roberts et al, 1992, Reilly et al, 1993), its usefulness for the determination of body composition in hospitalized individuals has not been established.

Serum concentrations of albumin, prealbumin, retinol binding protein, and transferrin are

frequently used to assess the visceral protein status. While some COPD patients show subnormal values, most have values within the normal range (Braun et al, 1986, Openbrier et al, 1983, Schols et al, 1989, Laaban et al, 1993). Although a reduction in visceral proteins has prognostic value, they are often preserved at the expense of somatic protein, and may reflect disease severity rather than poor nutritional status. Visceral proteins are influenced by the inflammatory response and as such may not accurately predict the nutritional status in acutely ill patients (DeMeo et al, 1992). Means of assessing the metabolically active tissues have to be made available to the nutritionist in order to properly evaluate nutritional status and institute the necessary therapy.

Depending on the population studied and the criteria used to document the nutritional status, between 19 and 60% of patients with COPD are malnourished. Bioelectrical impedance and isotope dilution methods need to be further explored as they might prove useful as noninvasive and more precise tools to assess the nutritional status of individuals. Nutritional indices suffer because investigators choose variables and cut-off points arbitrarily, making comparisons between studies more difficult. Until such time as nutritional indices are standardized and bioelectrical impedance or isotope dilution methods are readily available to the nutritionist in a clinical setting, body mass index in combination with skinfold measurements and midarm circumference, is the most useful and inexpensive measure of nutritional status in this clinical setting.

1.3 EFFECTS OF PROTEIN-ENERGY MALNUTRITION ON THE CLINICAL COURSE, HEALTH AND WELL-BEING OF PATIENTS WITH COPD.

1.3.1 Effects of COPD on the respiratory muscles

Although COPD has been defined as a disease affecting lung parenchyma and airways, it can have profound effects on the respiratory muscles (Ferguson, 1993). Under normal conditions, inspiration is active and expiration occurs passively with the relaxation of the inspiratory muscles and the elastic recoil of the lung. Major causes for respiratory muscle dysfunction in patients with COPD are increased airway resistance and hyperinflation of the lungs. In COPD, expiratory airflow is limited, causing air to be trapped in the lungs, and is responsible for most of the hyperinflation (Cherniack, 1991).

With increased airway resistance and hyperinflation, the work of breathing is markedly elevated, and COPD patients may breath at a volume that is one and a half to two times the normal value (Rochester, 1991). Hyperinflation causes the inspiratory muscles to operate in unfavourable conditions. Normally, maximal contractile force is generated at the muscle's resting length. As lung volume increases, the inspiratory muscles shorten and their ability to generate negative inspiratory pressure (PI_{max}) decreases. Hyperinflation also affects the geometry of the respiratory muscles. The diaphragm, the primary muscle of inspiration, assumes a dome shape that protrudes upward into the thoracic cavity. The tension developed in a tightly curved diaphragm is more effectively converted into transdiaphragmatic pressure which is necessary to move air into the lungs. With

hyperinflation, the diaphragm is flattened, increasing the radius of the curvature and decreasing the pressure generated. A flattened diaphragm may be incapable of generating any useful inspiratory pressure (Tobin, 1988).

Gas exchange is severely impaired in COPD and as a consequence, the level of minute ventilation needed to maintain arterial carbon dioxide pressure at normal levels can be two to three times normal (Rochester, 1991). Because of the destruction of the alveolar-capillary units, elastic recoil of the lungs is lost. In addition, hyperinflation also adversely affects the elastic recoil of the thoracic cage, which under normal conditions, assists the inspiratory muscles in inflating the lungs. This means that the inspiratory muscles must not only work against the elastic recoil of the lungs but also against that of the thoracic cage. The muscles of the abdominal wall and other accessory muscles are recruited to increase ventilation. Hyperinflation may also shift the ribs from their normal oblique position to a more horizontal position making it difficult for the inspiratory intercostal muscles to lift the ribs and expand the rib cage, potentially contributing to the abnormal rapid shallow breathing seen in COPD (Tobin, 1988).

1.3.2 Malnutrition and respiratory muscles

Thurlbeck (1978), investigated the relationship between body weight and diaphragm weight in 103 male and 81 female emphysematous lungs at autopsy. Diaphragmatic weight was linearly related to body weight in both males ($r= 0.76$, $p<0.001$) and females ($r= 0.77$, $p<0.001$) but showed a weak relationship to body length in male ($r= 0.37$, $p<0.05$) and female subjects ($r= 0.18$, $p<0.1$). An association with weight but not height

thus suggests that diaphragmatic weight is diminished in patients with emphysema.

A clearer picture emerges from another necropsy study carried out in 1982 by Arora and Rochester, who examined the effects of body weight on diaphragm muscle mass, thickness, and area in 72 adults without COPD, who died of various causes. Their principal finding was that in the six subjects whose body weights were greater than 120% IBW, the diaphragm muscle mass, thickness, area and length were 165, 129, 125, and 117% of normal respectively, whereas 14 undernourished patients, whose body weights were below 85% IBW, the values were 57, 73, 77, and 83% of normal respectively. A 30% reduction in body weight was associated with a 40% loss of diaphragm muscle mass. These findings suggest that changes in body weight during acute and chronic illness profoundly affect diaphragm muscle mass, thickness, area and length.

Following their study on the effects of body weight on diaphragm muscle mass, Arora and Rochester (1982) investigated the effect malnutrition has on respiratory muscle function. Sixteen poorly nourished (71± 6% IBW) and 16 well-nourished subjects (104±10% IBW) without pulmonary disease were studied, and the results clearly demonstrated that poor nutritional status was associated with severe respiratory muscle weakness. Respiratory muscle strength, assessed from the maximal inspiratory (PI_{max}) and expiratory (PE_{max}) pressures that can be generated by maximal voluntary effort, was significantly lower in the malnourished group compared with well nourished subjects (PI_{max} -35±14 cm H_20 versus -95±31 cm H_20; $p<0.001$) (PE_{max} 59±24 cm H_20 versus 151±52 cm H_20;$p<0.001$). The loss of strength was distributed evenly between inspiratory and expiratory muscles and was directly proportional to the degree of weight loss.

Rochester and Braun (1985) examining the determinants of PI_{max} in COPD noted that PI_{max}, measured at residual volume in patients with COPD, correlated significantly ($r=0.43$, $p<0.02$) with percent ideal body weight, proposing that, in addition to the mechanical disadvantage COPD patients experience, low body weight may be a contributing factor to low inspiratory muscle strength.

An interesting study carried out in 15 severely malnourished (63% IBW) patients with anorexia nervosa, demonstrated the beneficial effects that refeeding can have on diaphragmatic muscle function (Murciano et al,1994). Controls were not used in this study since withholding nutritional support from seriously malnourished subjects would be considered unethical. Diaphragmatic function was assessed using peak transdiaphragmatic pressure (Pdi_{stim}) generated during constant electrical phrenic nerve stimulation, and single maximal sniffs (Pdi_{sniff}) with at least 2 quiet breaths between each sniff such that peak transdiaphragmatic pressure was not sustained. Diaphragmatic contractility was depressed upon admission to hospital, (Pdi_{stim} 15.9±1.4 cm H_20; Pdi_{sniff} 65.4±5 cm H_20) but significantly improved with nutritional support by day 30 to 22.5±1.9 and 84.6±4.7 cm H_20, $p<0.001$ respectively. Although these patients were free of other diseases, and did not suffer any of the deleterious effects that COPD inflicts on diaphragmatic muscle function, the data demonstrate that the diaphragm is affected by malnutrition and diaphragmatic muscle function can be restored during refeeding.

1.3.3 Malnutrition and functional ability

The possible association of malnutrition and general functional ability in COPD has not

been studied in great detail. Gray-Donald and colleagues in 1989, examined the relationship between nutritional status and functional capacity in 128 severely obstructed COPD patients. Although a clear association of peak oxygen consumption as a measure of functional capacity (% VO_2 max, % predicted) and malnutrition was found, (<90% IBW, % VO_2 max 37.2±2.09, 90 to 119% IBW, %VO_2 max 47.0±2.19, >120% IBW, %VO_2 max 53.7±2.45; $p<0.01$ between the groups) activities of daily living, such as walking or perception of dyspnea and quality of life scores were not worse in the malnourished group than in normal or overweight subjects for the same degree of lung function impairment, implying a process of adaptation to the limitations COPD imposes on patients. Schols and coworkers (1993) reached a similar conclusion after evaluating the exercise performance, using a 12-minute walking test, in 255 stable COPD patients admitted to a pulmonary rehabilitation program. Malnourished patients (< 90% IBW) with relative preservation of fat-free mass were able to walk a similar distance in 12 minutes (~ 700 m) as normal weight patients (> 90% IBW).

1.3.4 Malnutrition and mortality

One of the most serious consequences of untreated malnutrition is mortality. Wilson (1989), in a retrospective analysis of 779 men with varying degrees of airflow obstruction and different body weights (<90, 90 to 110, >110% IBW) concluded that mortality, independent of FEV_1, was influenced by body weight. Mortality increased with decreasing body weight within each FEV_1 group. With FEV_1 <35% predicted, this relationship was not strong ($p=0.093$) but became stronger in men whose FEV_1 was

between 35 and 47% predicted (p=0.048), and even stronger in men whose FEV_1 was >47% predicted (p=0.007) supporting the belief that elements related to nutritional status may have a bearing on the course of COPD. In another study, (Gibbons, 1990) the role of nutritional status, measured by BMI and triceps skinfold, as predictors of mortality in 348 patients with COPD were examined and both significantly predicted survival in this group of subjects. Multivariate survival analysis revealed that the probability of surviving 2 years after the study fell to ~ 66% for the underweight group (body mass index less than 20). Normal weight (body mass index between 20 and less than 27) subjects' chances of surviving was 79%, whereas overweight subjects probability of surviving was 88%.

COPD places enormous demands on the respiratory muscles. The mechanical disadvantage and metabolic consequences of the disease increase the total work and cost of breathing greatly. Underweight patients have diminished respiratory muscle strength and mortality increases with decreasing body weight, independent of airflow obstruction, however, activities of daily living do not appear to be affected by malnutrition. Therapies focusing on strengthening respiratory muscles and maintaining a normal body weight throughout the chronic and acute phases of the disease should be part of every patients treatment so as to slow the progression of the disease and relieve the adverse effects of COPD.

1.4 PROPOSED CAUSES OF WEIGHT LOSS.

Weight loss and poor nutritional status appear to be common among a subgroup of

patients with COPD. Weight loss occurs when energy expenditure exceeds energy intake and theories regarding the weight loss in patients with COPD are diverse (Wilson, 1985). Weight loss may develop gradually as a result of the clinical deterioration of COPD, or it can occur during the many exacerbations of the disease, when energy intake in relation to energy expenditure is insufficient (Rogers, 1992, Fitting, 1992). The possible reasons for weight loss explored here are increased energy requirements, decreased dietary intake, hospitalization, and the metabolic effects of cytokines such as tumor-necrosis factor-alpha.

1.4.1 Increased energy requirements

In most relatively sedentary adults, the basal metabolic rate is the largest component (~60-70%) of energy expenditure with physical activity and metabolic response to food being responsible for the balance of total energy expenditure (FAO/WHO/UNU, 1985). In two famous starvation studies of weight loss basal metabolic rate decreased substantially in healthy persons. The Carnegie Experiment, (ref 9 in Wilson, 1985) where a total weight reduction of 10 percent was observed, an average decline in basal metabolic rate of 15 to 20 percent was recorded. The mean pulmonary ventilation also decreased by 12 percent and oxygen consumption fell by 18 percent. In another famous starvation study in Minnesota (ref 5 in Hoffer, 1994), subjects lost approximately 25 percent of their body weight over a 24 week period. The basal metabolic rate fell by 40 percent. Minute ventilation decreased from 4.82 to 3.35 L/minute, and the average oxygen consumption decreased by 31 percent, which are lifesaving measures to reduce energy expenditure. COPD does not appear to bestow this adaptive mechanism on the respiratory function.

The patient with COPD experiences reduced ventilatory muscle efficiency and hyperinflation, leading to increased work of the respiratory muscles to maintain adequate levels of ventilation (Tobin, 1988). Studies examining the energy requirements of COPD patients are summarized in table 2. Two studies focused on the oxygen consumption of the respiratory muscles. Donahoe (1989) reported that total resting oxygen consumption adjusted for body weight was significantly different among malnourished COPD patients, normally nourished COPD patients and control subjects. The control group's oxygen consumption was 3.20±0.2 ml O_2/min·kg (mean±SD), normally nourished COPD's oxygen consumption was 3.10±0.53 ml O_2/min·kg, while malnourished COPD subjects had significantly higher oxygen consumption 4.20±0.47 ml O_2/min·kg, $p<0.001$, however, no significant difference was present between the control group and the normally nourished group. The oxygen cost of ventilation was also significantly elevated in the malnourished group 4.28±0.98 ml O_2/L ventilation relative to the normally nourished group 2.61±1.07 ml O_2/L ventilation, $p<0.001$. Shindoh (1994) (not in table) reported a significantly higher oxygen consumption, (expressed as the log of change in total oxygen consumption/change in minute ventilation) of the respiratory muscles in COPD patients compared with age-matched normal subjects. The mean ratio of change in total oxygen consumption/minute ventilation among the 8 COPD patients was ~0.025, whereas the normal subjects' ratio was ~0.009, $p<0.001$. In a healthy subject, who is walking rapidly or performing light work, the oxygen consumption of the respiratory muscle represents 6 percent of total oxygen consumption. For COPD patients oxygen consumption can be between 35 percent of total oxygen consumption for eucapnic, and 50 percent for

hypercapnic individuals. These are extremely high levels of oxygen consumption by the respiratory muscles (Rochester, 1991). Because they use so much oxygen just for breathing, COPD patients have much less oxygen left for any physical activity. Five other studies (Goldstein, 1987, Fitting, 1989, Donahoe, 1989, Wilson, 1990, Schols, 1991b) used indirect calorimetry, a noninvasive method estimating oxygen consumption and carbon dioxide production, to determine resting energy expenditure (REE). Indirect calorimetry is simple to perform and results in reliable measurements of REE in normally nourished subjects (Ferrannini, 1988). REE was calculated using the equation of Weir (1949) REE = $[(3.941*VO_2) + (1.10*VCO_2)*1.44]$. The investigators compared the measured REE with REE predicted by the Harris and Benedict equation, adjusted for sex, age, weight and height. The mean results for malnourished COPD patients from each study are remarkably close: 116, 116, 119, 115 and 118 %predicted respectively, supporting the view that malnourished COPD patients have elevated REE, and an adaptation to weight loss seen in normal subjects is lacking in malnourished COPD patients.

The conventionally held theory of elevated REE is being challenged by two recent studies. Ryan (1993) and Sridhar (1994) reported measured REE compared with REE predicted by the Harris Benedict equation to be 94 and 104% respectively for malnourished COPD patients. Why these results differ is not entirely clear.

Donahoe (1989) and Wilson (1990) used a more invasive system to measure REE. Patients wore noseclips, and a mouthpiece was used to collect the gases. This method was shown to overestimate resting energy expenditure in patients with chronic lung

disease (Sridhar, 1994). Fitting (1989) used a ventilated hood which was made airtight around the neck and the additional discomfort could have been responsible for the higher REE. Goldstein determined resting energy expenditure three to five times throughout a 24-hour period, which no longer represents resting energy expenditure in the postabsorptive state. The studies by Ryan and Sridhar are not without their limitations. Ryan only used 10 subjects and no control group, and 3 of the subjects had requirements of 110% predicted. The small sample (n=6) studied by Sridhar, and the fact that energy expenditure measurements were taken from a single 15 minute period only, while most studies used measurements over a thirty minute period cast doubt on the reported results.

In a well designed study by Schols (1991b), 102 subjects, 34 weight losing, 34 weight stable, and 34 control subjects were investigated. The weight losing (a decrease in body weight of ≥ 10% of usual weight within 6 month prior to study) and wiehgt stable (no gain or loss ≥ 1 year prior to study) were recruited from a pulmonary rehabilitation center, and all were in stable pulmonary and cardiac condition. The control subjects were healthy men and women of similar ages and living in the same area as the patients. All control subjects had stable weight. Weight losing COPD patients exhibited higher resting energy expenditure (118±17% predicted) relative to weight stable (110±11 %predicted, $p<0.05$). Both groups were significantly higher than healthy controls (104±6% predicted, $p<0.05$). Resting energy expenditure adjusted for fat-free mass was significantly higher in weight losing than in weight stable patients (~1,640 kcal versus ~ 1550 kcal, $p<0.05$). The author postulated that a disease related hypermetabolism plus lack of adaptation to

weight loss are responsible for the elevated energy expenditure in weight losing COPD patients.

The need to accurately determine energy requirements is important because appropriate nutritional support given to patients can both prevent and treat a malnourished condition. The Harris Benedict equation, customarily used in a clinical setting, as a substitute for indirect calorimetry, was reevaluated by Roza and Shizgal (1984). The authors main findings were that the Harris Benedict equation estimates REE in normal subjects with a precision of ±14%. Also, REE is directly related to the size of the body cell mass, the metabolically active component of body composition responsible for all the oxygen consumption and carbon dioxide production, and with a constant body cell mass REE is independent of age and sex.

In malnourished individuals, the Harris Benedict equation is thought to be an unreliable substitute for REE, as it underestimates the needs by ~ 20% (Roza and Shizgal, 1984). Moore (1988) derived COPD specific regression equations for estimating REE. A group of 43 stable COPD patients with FEV_1/FVC <60% predicted were recruited from routine clinic visits. REE was measured using indirect calorimetry after an overnight fast and a regression equation using weight only was developed for both men and women. The REE measured by indirect calorimetry was compared with a number of prediction equations; the Harris and Benedict equation (ref 14 in Moore, 1988), two equations derived by Quebbeman and Ausman (ref 13 in Moore, 1988), and a nomogram by Wilmore (ref 14 in Moore, 1988). A prospective evaluation of the COPD specific regression equation was performed in a second group of 57 similar subjects. The REE obtained from the COPD

specific equation underestimated the requirements by 73 ± 279 kcal compared with REE derived from indirect calorimetry in the prospective analysis of fifty-seven stable COPD patients. The other prediction equations underestimated the REE by the following amounts: the Harris and Benedict equation by 352 ± 262 kcal, the Quebbeman and Ausman equations underestimated REE by 208 ± 273 and 246 ± 276 kcal respectively, and the nomogram underestimated the REE by 329 ± 268 kcal. The COPD specific regression equation was also tested in 24 unstable, hospitalized COPD patients, 15 of whom were intubated. The COPD specific regression equation underestimated the REE by 108 ± 297 kcal compared with REE measured by indirect calorimetry. The other prediction equations underestimated the REE by the following amounts: the Harris and Benedict equation by 342 ± 296 kcal, the Quebbeman and Ausman equations by 245 ± 284 and 284 ± 305 kcal respectively, and the nomogram underestimated requirements by 339 ± 314 kcal. This COPD specific equation may be a convenient alternative for the determination of REE, as it only requires body weight as a variable.

1.4.2 Decreased dietary intake

Since weight maintenance depends on an equilibrium in energy balance, ie Energy input = Energy output, even a small but steady decrease in energy intake will lead to weight loss. Unfortunately, studies designed to investigate dietary intake in patients with COPD are few. Hunter in 1981 used a "diet history" to assess the intake of 36 subjects, most having severe COPD. The energy intake in the total group was varied, ranging from 1,096 to 4,401 kcal/day with a mean of 2,535±878 kcal. The protein intake was also

variable ranging between 38.0 to 160.0g/day, with a mean intake of 87.1±31.2 g/day. Despite intakes for energy and protein for most subjects that was higher than recommendations in 1974 for males older than 50 years of age, nine (25%) reported weight loss of less than 10%, and 16 (44%) reported weight loss greater than 10% for the previous year. Keim (1986) undertook a dietary evaluation of 64 subjects with moderate or severe COPD using a 3-day dietary record. Unfortunately no data on the actual intake of energy, protein, fat, and other nutrients were given. The Harris and Benedict equation was used to predict basal energy expenditure, and adequacy of intake was assessed by comparing mean intake with that predicted by the Harris and Benedict equation. The more malnourished subjects (<75% IBW) had the higher the energy (193±21% of basal energy expenditure) and protein intakes (208±19%). Subjects with normal weight, (>95% IBW) had significantly lower energy and protein intakes, namely 127±11 and 128±12% ($p<0.05$) of calculated needs respectively. The Harris and Benedict equation is known to underestimate basal energy expenditure in malnourished subjects by ~ 20% (Roza and Shizgal, 1984) therefore, caution is necessary when interpreting results from this study.

The only other direct assessment of diet comes from a nutritional intervention study carried out by Efthimiou (1988). Fourteen poorly nourished (<90% IBW) and 7 well nourished (>90% IBW) COPD patients underwent a 7-day dietary assessment on entry to the study, and every month thereafter for a total of 9 months. The poorly nourished groups energy intakes were significantly lower than the normally nourished group, 1,410 kcal/day versus 2,208 kcal/day ($p<0.05$) at the beginning of the study. Protein intake was

also lower, 51.1 g versus 89.8 g protein/day ($p<0.05$). While the absolute energy and protein intakes differed significantly between the groups at the beginning of the study, the average energy intakes based on kg of body weight were higher in the poorly nourished group (32 kcal/kg) compared with the normally nourished group (29.4 kcal/kg). Protein intakes for both groups were similar (1.19 g/kg). Why some COPD patients become malnourished is not clear. Efthimiou's study offers some insight. Subjects had similar airway obstruction, and all were studied in a stable phase of their disease, and none was taking glucocorticosteroids. Weight in the poorly nourished group and the adequately nourished group was significantly different at the beginning of the study 48kg versus 75 kg ($p<0.05$), however, weight did not change over the course of the study in the undernourished group. From these results one could speculate, that these subjects are able to maintain energy balance over a given period of time, and some other event might be responsible for increased energy requirements.

Data on energy and protein intakes of hospitalized COPD patients are rare. In an unpublished study, (Haddad, 1993) energy intakes for 6 males averaged 1,617±431 kcal/day (mean±SD), while 10 women consumed 1,321±438 kcal/day. Protein intakes were 66±29 and 54±19 g/day respectively. Nitrogen balances carried out in seven patients, four of whom were in negative balance, one was in balance, and 2 exhibited slightly positive balances, indicated that the level of energy and protein was inadequate for most.

Because of the paucity of literature available on dietary intake among COPD patients, and the poor study design of some (Hunter, 1981, Keim, 1986), no valid support can be given

to the theory that a decreased dietary intake per se might be responsible for the weight loss seen in some COPD patients. A more likely scenerio is one of drastically increased energy requirements during periods of instability.

1.4.3 Hospital associated malnutrition

One of the clinical problems in patients with advanced COPD, regardless of whether it is predominantly emphysema or chronic bronchitis, is frequent episodes of acute reversible airway obstruction. Irritants from either an exogenous or/and endogenous source can result in airway narrowing, edema formation, increased mucus production, and stimulation of inflammatory and immune cells (Gerard, 1991). These episodes, which are likely triggered by viral infections in most instances, can result in frequent hospitalizations, where a deterioration in nutritional status is a likely consequence. Although not previously reported in COPD patients, such a deterioration has been documented in a general hospital population (Weinsier et al, 1979, Constans et al, 1992, Gamble Coats et al, 1993, McWhirter and Pennington, 1994).

Weinsier (1979) assessed the nutritional status of 134 patients entering hospital with a variety of acute and chronic illnesses and reassessed the nutritional status of 44 patients who remained in hospital 2 weeks or longer. A scoring system, likelihood of malnutrition, combining weighted anthropometric and biochemical measurements believed to be both specific and sensitive indicators of malnutrition, was used to classify patients. Patients were grouped according to the likelihood of malnutrition being major, intermediate or minor on admission and 2 weeks later. Of the 44 patients who remained

in hospital for more than 2 weeks, the likelihood of malnutrition was major in 28 of the 44 (62%) patients on admission. A significant deterioration in weight, triceps skinfold, arm muscle circumference, lymphocyte count and hematocrit ($p<0.01$) occurred in 31 of the 44 (69%) follow-up patients. Also, patients with a higher likelihood of malnutrition score on entry, stayed significantly longer in hospital than did patients with a low likelihood of malnutrition score (20 days versus 12 days, $p<0.05$). They also had an increased mortality rate (13% versus 4%, $p=0.10$). Gamble Coats (1993) 12 years later, at the same hospital, using the same methods and scoring system, re-examined the prevalence of hospital malnutrition. Forty-eight patients staying 2 weeks or longer were assessed. The likelihood of malnutrition score comprising plasma folate, plasma ascorbate, %IBW, triceps skinfold, arm muscle circumference, lymphocyte count, serum albumin, and hematocrit improved with stay in the later study, (a 7 point decrease) whereas in 1979, the mean score deteriorated (a 2 point increase) $p=0.01$, suggesting a slight improvement in nutritional care during more recent hospitalizations at their centre. Constans et al (1992) evaluated the changes in nutritional status during hospital stay among elderly, aged 70 years and over. Twenty-one men and 32 women were hospitalized for a variety of reasons and stayed 15 days or more. Twenty-six healthy men and 36 women, aged 70 years and over were used as controls and recruited from registered students of the University of the Third Age. They provided midarm circumference, triceps skinfold, and blood samples for baseline measurements only. Either midarm circumference below the 10 percentile of midarm circumference distribution in 26 healthy controls or serum albumin below 3.5g/dl constituted moderate

protein energy malnutrition. If both parameters were below cut-off points, protein energy malnutrition was considered severe. Both midarm circumference and serum albumin level decreased significantly over the first 15 days of stay in hospitalized patients ($p<0.05$). A step-wise discriminant-function analysis revealed that age as well as low midarm circumference, triceps skinfold, albumin and prealbumin were predictors of mortality.

Body mass index is thought to be too insensitive an indicator of protein energy malnutrition as it cannot distinguish between loss of fat or muscle (Gibson, 1990). Body mass index and changes in weight were shown to be useful, albeit crude indicators of changes in nutritional status during hospitalization (McWhirter and Pennington, 1994). The nutritional status of 100 consecutive admissions each from general and orthopaedic surgery, general medicine, respiratory medicine and medicine for the elderly was determined from BMI, triceps skinfold, midarm circumference, and weight loss before admission to hospital. One hundred and twelve patients were reassessed on discharge. Seventeen of the nineteen patients classified as mildly undernourished (body mass index <20) on admission, recorded a mean weight loss of 5.3% during their hospital stay, two gained on average 3.4%. Of nineteen moderately malnourished, (body mass index <18) thirteen lost on average 9.7% of their body weight, while 6 gained 4.4%. Eleven severely malnourished (body mass index <16) patients lost 6.4% of their pre-admission weight, whereas six gained 8.1%. Seven of the fourteen patients that gained weight, did so because they received nutritional support in the form of enteral or parenteral feeding. While no direct documentation of changes in nutritional status among hospitalized COPD patients is available, a deterioration in nutritional status during an acute exacerbation is

a likely developement.

Wilson (1985) proposed a stepped decline in weight and lung function, arguing that patients with COPD will function reasonably well and maintain their weight (Efthimiou, 1988) until an illness leads to elevated energy requirements which are not being met. This scenerio could occur many times during the course of COPD, resulting in periods of inadequate energy intake relative to energy requirement. The weight loss that follows is not necessarily regained upon recovery (Rogers et al, 1992). In addition, more calories are needed to maintain body cell mass, and depleted body cell mass is more slowly restored in malnourished elderly subjects (Shizgal et al, 1992). Any loss in lean body mass during an acute exacerbation would be difficult to regain as energy needs are likely to be very high for the addition of lean body mass. Glucocorticosteroids, a standard treatment modality during an exacerbation, have catabolic effects on protein metabolism (Truhan, 1989).

The only observation that weight loss occurs during an exacerbation comes from a retrospective examination of weight subsequent to a refeeding trial (Rogers et al, 1992) and weight loss appeared to be associated with clinical exacerbations. During the 3 months following the trial 29 exacerbations were recorded with a mean weight loss of 1.5kg/exacerbation. Many but not all subjects, regained some of the weight lost during the acute phase.

1.4.4 Tumor necrosis factor-alpha and weight loss

A COPD patient may be admitted to hospital with an acute exacerbation, complaining of increased cough, excess sputum production and increased dyspnea. This acute phase may be triggered by an infection or environmental stimuli (e.g. dust, pollution, cigarette smoke, occupational irritants). During the body's response to infection, injury or inflammation, cytokines, a family of glycoproteins, are released by immunocompetent cells (Tracey and Cerami, 1993). Cytokines can be beneficial to the host as growth factors in wound healing, or as a cellular cytotoxin against pathogens, however, when produced in excess they can be harmful, and are capable of killing the host either acutely (as in septic shock) or chronically (as in cachexia). The net biological effect of tumor necrosis factor-alpha and other cytokines is determined by a complex interaction with other factors. For example glucocorticoids, having potent anti-inflammatory properties, decrease the quantity of tumor necrosis factor produced. Chronic infection and cancer, in contrast, enhance the effects of tumor necrosis factor (Tracey and Cerami, 1994).

Recent experimental studies have focused on the belief that tumor necrosis factor-alpha, a cytokine, produced primarily by macrophages, and through broad physiologic actions, can lead to a chronic state of wasting, malnourishment and ultimately death (McNamara, 1992). Many cancer patients experience cachexia, an affliction characterized by extreme weight loss, anorexia, catabolism of vital protein and energy stores, and anaemia (Tracey and Cerami,1992). The difference between unstressed starvation and cachexia is that in starvation a protective mechanism leads to the conservation of whole-body protein with a preferential catabolism of lipid, but in cachexia, protein catabolism continues unimpeded

(Tracey and Cerami, 1992).

Evidence from animal studies suggests that chronic exposure to cachectin, as is likely to occur in cancer or chronic disease, participates in the metabolic response of cachexia (Tracey et al, 1988). Female rats, during a study period of 7-10 days, were given twice daily injections of cachectin. Controls and pair-fed controls were handled similarly except that human albumin, instead of cachectin, was injected. No animals died during the study period. Significant reduction in food intake was observed in the cachectin injected animals compared with controls receiving albumin injections. The cachectin treated animals had statistically significant weight loss ($p<0.05$) as compared with albumin-injected controls. Significant depletion of whole-body lipid and protein stores ($p<0.05$) was associated with cachectin administration.

The effect of an eight day tumor necrosis factor-alpha treatment on overall protein metabolism in the liver, diaphragm, heart, and leg muscles was studied in rats (Llovera, 1993). No weight loss occurred. Tumor necrosis factor-alpha resulted in increased protein synthesis and protein degradation in all types of tissues. A greater increase in the protein degradation resulted in a reduced protein accumulation, suggesting enhanced muscle wasting in experimental animals but not resulting in any measurable weight loss.

Studies investigating the possible involvement of tumor necrosis factor-alpha in the unexplained weight loss in COPD are beginning to appear in the literature (Di Francia et al, 1994). Tumor necrosis factor-alpha levels in serum of 30 stable, male COPD patients were measured. Sixteen subjects had unintentionally lost weight during the previous year,

(81% of IBW) and their tumor necrosis factor-alpha levels were ten times higher (70.2±100 picograms/ml) (mean±SD) than the the levels found in fourteen weight stable (121% of IBW) subjects (6.7±6.4 pg/ml, $p<0.001$). Tumor necrosis factor-alpha serum levels in weight stable subjects did not differ from those of healthy subjects (7.8±3.9 pg/ml). The two groups of COPD subjects had similar airflow obstruction and blood gas impairment. None of the subjects had been receiving steroids during the preceding 3 months, and subjects with obvious respiratory or nonrespiratory infection were excluded. Although this study was observational in nature and no cause and effect relationship can be inferred, it is the first study to implicate higher serum tumor necrosis factor-alpha levels as a possible reason for weight loss in patients with COPD.

Weight loss in COPD is a poor prognostic sign, and it is likely that no single factor is responsible for the weight loss seen in a subpopulation of COPD patients. The energy cost of breathing is elevated, and energy expenditure is conceivably even greater during an exacerbation of the disease. When possible, REE should be measured using indirect calorimetry since the Harris Benedict equation is unreliable in malnourished individuals. Hospitalization per se can contribute to a deterioration of nutritional status, and a further insult to muscle mass can occur because of chronic overproduction of cytokines during the inflammatory process resulting in the continuous catabolism of body mass in COPD patients.

1.5 NUTRITIONAL SUPPORT IN COPD

Malnutrition is an important clinical problem in a subgroup of patients with COPD, and progressive weight loss is associated with a deterioration of lung function (Goldstein, 1986) and an increase in mortality (Wilson, 1985). Providing nutritional support to malnourished patients is important and the aim of such interventions in COPD patients should be the maintenance or improvement of pulmonary function and respiratory muscle strength.

1.5.1 Nutritional intervention studies in malnourished COPD patients

As can be seen from table 3, a number of controlled studies have assessed nutritional therapy either among in-patients or among out-patients with mixed results.

Three studies (Wilson et al, 1986, Whittaker et al, 1990, Rogers et al, 1992) have shown, that under well controlled experimental conditions, short-term (14-21 days) nutritional therapy will result in weight gain and improvements in respiratory muscle strength in stable, malnourished subjects. Wilson studied six malnourished subjects, admitted to a clinical research unit, and a mean weight gain of 3 kg and improvements in maximal inspiratory pressure [-31.7±4.0 cm H_2O to -45.2±6.4 cm H_2O, $p<0.005$, (mean±SEM)] were observed. Total caloric intake although greater than 1.5xREE in 3 subjects and enough to meet energy needs in the other 3 was not specified. A control group was not studied making it unclear whether general improvement in their condition was due to the extra attention subjects received or to refeeding. Whittaker carried out a randomized controlled refeeding trail in 10 malnourished subjects. The six subjects randomized to receive 1000 kcal overnight nasoenterically above their usual intake, were able to record

a mean weight gain of 2.4 kg. They also showed improvements in maximal expiratory pressure (92±5 cm H_2O to 126±6 cm H_2O,$p<0.05$). The remaining 4 control subjects were sham fed (100 kcal) and no improvements occurred. Rogers (1992) conducted a randomized refeeding trial with 27 malnourished subjects. Treatment patients received nutritional supplementation for 3 weeks and were followed for an additional 3 months. Caloric intake in the treatment group was greater than 1.7*REE, protein intake was 1.5g/kg body weight. A mean weight gain of 1.7 kg during the inpatient phase was achieved, while a loss of 0.5 kg was recorded in the control group. Handgrip strength improved 5.5kg-force for the intervention group and declined by 6.0kg-force in the control group ($p=0.01$). Maximal expiratory pressure improved by 14.9 cm H_2O for the intervention group and dropped 9.2 cm H_2O in the control group ($p=0.03$). During the 3-months follow-up, both intervention and control subjects lost weight, which corresponded to disease exacerbations. Subjects registered a mean weight loss of 1.5kg/exacerbation. Many subsequently regained some of the weight lost during an exacerbation.

Of the five outpatient refeeding trials, four did not observe any improvements in lung function or respiratory muscle strength over periods ranging from 8 weeks to 4 months. The most likely explanation for some of the negative results, was the small increase in additional calories (between ~ 275 and 425 kcal) subjects consumed.

In one study (Knowles et al,1988), half the subjects were normally nourished and probably unable to increase their intake further. Otte (1989) used a placebo controlled, randomized, double-blind design, and 13 treatment subjects achieved a significant mean

weight gain of 1.5kg, $p<0.01$ over a period of 13 weeks. No changes in pulmonary function and respiratory muscle strength were observed. Energy intakes were much higher (~2,319±113 kcal) than in most other studies summarized in table 2. Nevertheless, seven (7/28) subjects had an acute exacerbation during the trial, 3 were treated with glucocorticosteroids, which are known to be catabolic. Unfortunately data were not analyzed without these patients, and the effect of these exacerbations on the outcome is not known. Weight loss during acute exacerbations has been reported (Rogers et al, 1992), and could have diminished weight gain and wiped out any possible improvements in respiratory muscle strength.

Lewis et al (1987) and Sridhar et al (1994) observed no improvements in weight, pulmonary function or respiratory muscle strength in their subjects. Their additional intake (~ 275 kcal and 425 kcal respectively) was modest and presumably insufficient to show any changes in measured parameters.

The one successful refeeding trial carried out in COPD outpatients was a well-designed and well-controlled study by Efthimiou and associates (1988). Seven malnourished subjects were randomized to receive a supplement, while seven poorly nourished and seven well nourished COPD patients followed their normal diet for 9 months. Baseline intakes were ~ 1,429 kcal for treatment subjects, 1,410 kcal for the seven malnourished controls, and significantly higher 2,208 kcal ($p<0.05$) for the 7 in the well nourished group. Treatment subjects received a high calorie/high protein supplement for 3 months, significantly increasing their usual intake by ~ 690 kcal and ~ 29 g protein/day, $p<0.05$. A mean weight gain of 4 kg in the treatment group was associated with small

improvements in maximal inspiratory pressure (-45.7 cm H_2O to -53.1 cm H_2O,$p<0.05$) and maximal expiratory pressure (78.7 cm H_2O to 84.0 cm H_2O,$p<0.05$). Grip strength improved by 1.9 kg and walking distance increased from 414 m to 467 m ($p<0.05$).

In a more recent randomized supplementation trial in elderly (>65 years) patients recovering from chest infections, treatment subjects received 500 ml of Ensure/day for a 1-month period after discharge from hospital (Woo, 1994). Patients were not specifically identified as having COPD, however, 67/81 suffered with chronic lung disease and 32/81 were treated with glucocorticosteroids. After one month of supplementation, body mass index improved in both men (19.33 to 20.03, $p<0.05$) and women (19.99 to 20.46, $p<0.05$) over the control group, but subjective measures of health and well-being, activities of daily living, appetite, and life satisfaction improved in both groups over a 3 months period, reflecting an overall recovery from illness rather than the effect of supplementation. Supplementation led to a significant increase in food intake in the treatment group 1,809±650 versus 1,449±617 kcal in the control group, $p<0.05$ after one month, but by 3 months follow-up, both the supplemented and control groups had similar intakes 1,452±645 versus 1,449±617 kcal. Difficulty in sustaining higher intakes after the 3 month supplementation period was completed was also observed in Efthimiou's study.

What becomes clear is that under tightly controlled conditions, and given enough energy and protein, malnourished COPD patients can gain weight and show improvements in respiratory muscle strength, handgrip strength, and walking distance. Ambulatory outpatients are more difficult to study. While Efthimiou's study demonstrated the

beneficial effects of nutritional therapy in an outpatient population, a heavy burden is placed on the participants over a long period of time; adherence to protocol, accurate assessment of intake, recurrent illnesses are some of the obstacles investigators have to overcome if quality of life and survival are to be improved in a substantial number of malnourished COPD patients.

1.6 USE OF GLUCOCORTICOSTEROIDS IN THE TREATMENT OF COPD

1.6.1 General adverse effects of glucocorticosteroids

Oral or intravenous therapy with glucocorticosteroids is a common strategy during an exacerbation of COPD. Their anti-inflammatory and immunosuppressive properties are well established, and are responsible for their extensive use in COPD, and other inflammatory diseases (Saag et al, 1994, Picado et al, 1990). The side effects of these potent drugs are well documented and include centripetal obesity with peripheral muscle weakness, fluid retention, leucocytosis, osteoporosis with secondary fractures, glucose intolerance, infections, peptic ulcer disease, gastrointestinal bleeding, and cataracts (Lukert, 1990; Saag et al, 1994). The effects of glucocorticosteroids on carbohydrate, protein and fat metabolism are well known. They promote gluconeogenesis by both peripheral and hepatic actions, resulting in elevated glucose levels in the plasma. An increased resistance to insulin occurs, inhibiting the utilization of glucose in the peripheral tissues. The effects on protein metabolism are indicated by an increase in skeletal muscle

protein breakdown, resulting in reduced muscle mass, thinning of skin, reduction of protein matrix of bone followed by calcium loss, and a negative nitrogen balance (Sherwood, 1989). They also appear to inhibit incorporation of amino acids into muscle protein. One of the well established effects of glucocorticosteroids on lipid metabolism is the dramatic redistribution of body fat, with accumulations of fat in the supraclavicular, (buffalo hump) truncal, and facial areas (moon face), and a loss of fat from the extremities.

1.6.2 Effect of glucocorticosteroid therapy on respiratory muscle function

Respiratory muscle dysfunction is a major repercussion of COPD and contributes to morbidity and limits activities of daily living. Glucocorticosteroids are frequently used to treat an exacerbation of COPD, and to determine whether they contribute to the abnormal respiratory muscle function or how steroids might affect respiratory muscle function has been the focus of research in recent years (Gallagher, 1994).

The diaphragm, being the most important inspiratory muscle in mammals, and thought to be more resistant to glucocorticoid-induced myopathy than skeletal muscle, was the focus of a study carried out in rats (Lieu et al, 1993). Rats received between 0.5 - 2.0 mg prednisolone/kg·day for 10 days, at which time they were anaesthetized and tissues were removed. Diaphragmatic weight loss ranged from 3.8 to 17%, whereas muscle weight loss in the plantaris ranged from 0.4 to 25% in the prednisolone treated group. Although weight loss ranges were similar, the difference in the slope of the prednisone dose-curve suggests that the diaphragm is more resistant to steroid-induced myopathy than

the less active locomotor muscle. This does not suggest that the diaphragm is immune to muscle myopathy. In humans, it would be difficult to separate the effects of steroid therapy on the diaphragm from the underlying disease before autopsy. Other measurements are used to evaluate the effects of steroids.

Two studies examined the effects of glucocorticosteroids in volunteers without COPD (Wang et al, 1991). In a double-blind, placebo controlled study, 16 healthy men aged 19 to 39 received orally 20 mg of prednisone daily for a period of 2 weeks. No significant changes in any measure of respiratory muscle function were recorded in either group, and no significant differences were found between the two groups. The results of this study imply that glucocorticoids in low dosage and for short durations have no deleterious effects in healthy adults, however, they may not be applicable to patients with chronic inflammatory disease, where higher doses for longer periods of time are more frequently used (Gallagher, 1994).

The effects of prolonged glucocorticosteroid treatment on respiratory and skeletal muscle function was evaluated in 34 oral steroid-dependent asthmatics (Picado et al, 1990). Their average daily dose of prednisone was 11.9±3.7 mg, and length of treatment averaged 7.9±4.6 years, while age and sex-matched asthmatics taking no glucocorticosteroids acted as controls. While the steroid-dependent asthmatics were significantly more obstructed, (FEV_1 54.1±15.8% predicted) than the control group (73±22% predicted; $p<0.001$), no differences were found in maximal inspiratory or expiratory muscle force or in skeletal muscle force between the two groups.

In another study (Weiner et al, 1993) 8 patients received high doses of prednisone

(61.3±7.4 mg/d) for non-pulmonary diseases for 8 weeks. Doses were then tapered down to complete withdrawal within 6 weeks. Lung and respiratory muscle function measurements were performed upon entry, every 2 weeks after administration of glucocorticosteroids and up to 3 months. Tests were repeated following the complete withdrawal of the drug. Patients had normal lung and respiratory function on entry, but developed severe inspiratory weakness during treatment, dropping from -126.9±9.6 cm H_2O to -86.5±7.4 cm H_2O, $p<0.0001$ by week 8. Baseline inspiratory muscle strength was regained only 6 months after treatment stopped, demonstrating a long recovery period from steroid-induced muscle weakness. However, this was not a controlled trial, and the underlying diseases (kidney, thyroid) could have made these patients particularly susceptible to steroid myopathy.

Decramer (1994) evaluated 21 patients admitted to hospital with an exacerbation of COPD or asthma, requiring intensive steroid treatment. Patients were evaluated 10 days after admission for an acute exacerbation in clinically stable condition. An average daily dose of corticosteroids, taken during the previous 6 months, was calculated. This included steroid treatment during exacerbations of their disease. A significant correlation between average daily dose of glucocorticosteroid, calculated for the previous 6 months, and maximal inspiratory muscle strength ($r= -0.50, p<0.05$) was found but no significant correlation existed between muscle forces and steroid usage during the acute phase in hospital, implying that any possible reduction in muscle strength was reversed 10 days after admission.

COPD patients were analyzed separately and after adjusting for age, sex, disease category,

and body weight, multiple linear regression demonstrated that the average daily dose was a significant predictor of quadriceps force and maximal inspiratory pressure, independent of other pulmonary function or anthropometric variables on day 10 of admission. Since no preadmission strength measurements were available, it is impossible to say whether respiratory muscle strength or quadriceps force had returned to normal, as the investigators speculated. It is unclear how long it would take for muscle function to recover completely after an exacerbation and steroid treatment, but if Weiner's study is any indication, it would certainly take more than 10 days. The study by Decramer is interesting, and will hopefully inspire other investigators to undertake longitudinal, controlled trials.

1.6.3 Effects of glucocorticosteroids on bone

Other equally disturbing effects of high glucocorticosteroid doses are overshadowed by the attention given to the respiratory muscles, but need to be considered since they are equally debilitating. The deleterious effects of glucocorticosteroids on bone are well recognized. Steroid-induced osteoporosis in asthmatics and those with rheumatoid arthritis has been reported for many years (Adinoff and Hollister, 1983, Worth, 1994, Saag et al, 1994, Laan et al, 1993, Roubenoff et al, 1990).

Adinoff (1983), in a retrospective study, examined the hospital charts of 128 asthmatics requiring long term steroid treatment, averaging 30 mg for at least 3 years, and compared these with 54 age and sex-matched asthmatics who used steroids intermittently. Fourteen of the 128 patients (11%) had a total of 58 documented fractures. No fractures occurred

in the control group. The retrospective nature of the study does not allow one to draw conclusions about the relation between dose or duration and fracture, however, the relationship between steroid use and fracture was clinically important. They then examined and compared prospectively, 30 asthmatics, 19 receiving long-term steroid treatments and 11 matched for age, sex, and disease severity who received intermittent treatment. Eight of nineteen patients receiving long-term glucocorticosteroids had spontaneous fractures. No fractures were diagnosed in the intermittent glucocorticosteroid users. Also, only patients requiring long-term glucocorticosteroid treatments had diminished bone density, suggesting that treatment with glucocorticosteroids, and not the disease itself, was responsible for the decreasing bone mass in asthmatics receiving long-term treatments.

The extent of glucocorticoid-induced bone loss and the effects of treatment with vitamin D, calcium, and a diphosphate were examined in a randomized clinical trial of 40 stable asthmatics, with an average age of 55 years, receiving more than 10 mg prednisone equivalent for an average of 7 years (Worth, 1994). Therapy with calcium, vitamin D, and ethane-1-hydroxy-1,1-diphosphonate led to a significant 5% increase in bone mineral density during the 6 months of the trial in the treatment group but decreased by 4.3% in the control group ($p<0.01$). The number of thoracic or lumbar vertebral fractures at 6 months was not significantly different between the groups. However, radiologically visible new fractures were observed in 4 patients in the control group, while none was observed in the treatment group. Similar decreases in bone mineral density with low dose glucocorticoids (10mg prednisone) were observed by Laan (1993) in patients with

rheumatoid arthritis, despite favorable effects on disease activity (measured by a composite index consisting of the erythrocyte sedimentation rate, the Ritchie articular index, the number of swollen joints, and a visual analogue scale for general health), and functional capacity.

1.6.4 Effects of glucocorticoids on nitrogen balance

The catabolic effects of high-dose glucocorticosteroids were evident in 9 subjects despite adequate food intake, aged 21 - 68, admitted to hospital with flare-ups of rheumatoid arthritis (Roubenoff et al, 1990). The study consisted of 3 periods, a wash-out period of 3 days, which was followed by 3 days of 1000 mg methylprednisolone/day and a period of 4 days after treatment. The mean nitrogen balances were -0.89±1.38 g nitrogen/day (mean±SEM) during the wash-out period. While patients improved clinically with therapy, the nitrogen balances during 3 days of treatment significantly deteriorated to -5.77±1.3 g nitrogen/day, $p<0.0001$, and was still negative 4 days after therapy, -3.54±1.38g nitrogen/day, $p<0.01$. Patients' energy intake increased spontaneously from 40.3±6.8 kcal/kg during the wash-out period to 46.8±6.2 kcal/kg during the treatment period and decreased to 44.6±5.9 kcal/kg after the treatment period. Protein intake was approximately 1.6 g/kg throughout the study. Whether the catabolic effects of glucocorticosteroids on protein metabolism can be averted was investigated in 15 patients, receiving between 70 and 120 mg of prednisone per day for 10 to 14 days, requiring haemodialysis after renal transplantation (Cogan et al, 1981). Six additional patients on

dialysis not receiving prednisone but recovering from comparable surgical procedures were used as controls. Seven prednisone treated patients received a low protein (0.73± 0.03 g protein/kg·day), low calorie diet (20±2 kcal/kg·day), whereas 8 prednisone treated patients consumed a high protein (1.30±0.06 g/kg·day), high calorie diet (33±3 kcal/kg·day). Control patients received 0.89±0.10 g protein/kg·day and 23±4 kcal/kg·day. The net protein catabolic rate, derived from the sum of urea nitrogen generation and non-urea nitrogen generation, was calculated for all patients. The net protein catabolic rate for the control group was not significantly different from dietary protein intake (0.87±0.11 g/kg·day), thus patients were considered to be in nitrogen balance. In contrast, the prednisone treated group ingesting a low protein/calorie diet not only had a significantly higher protein catabolic rate (1.45±0.12, $p<0.001$) than the control group, the protein catabolic rate was significantly different from zero (-0.72±0.12 g protein/kg·day, $p<0.001$) resulting in a negative nitrogen balance. The increased protein intake (1.30±0.06 g/kg·day) by the 8 prednisone treated patients was sufficient to compensate for the nitrogen loss, as patients were judged to be in nitrogen balance.

The negative nitrogen balance induced by gluocorticosteroid therapy is an important indicator of lean body mass depletion. The deleterious effects on bone are well recognized and therapies to oppose the steroid-induced bone loss in asthmatics are being investigated. The possibility of steroid induced respiratory myopathy and general muscle weakness in COPD needs to be clarified and brought to the attention of clinicians prescribing them.

1.7 NITROGEN BALANCE TECHNIQUE

In light of the prevalence of malnutrition and frequent hospitalization of COPD patients, the importance of nutritional support in such patients becomes intuitively obvious, but is difficult to accomplish. Nitrogen balance can be used to detect changes in body protein on a day-to-day basis during nutritional support and to indicate the severity of metabolic stress (Mackenzie et al, 1985).

Nitrogen balance requires that nitrogen intake and output are accurately determined. In hospitalized patients, nitrogen balance should be carried out after an equilibrium period, to allow patients to adjust to changes in protein intake. The length of readjustment period required depends on the relative change in protein intake (Gibson, 1990). For patients receiving a standard hospital diet, the relationship of protein ingested divided by 6.25 (one gram of nitrogen excreted represents the metabolic degradation of 6.25 grams of protein) can be used to calculate nitrogen intake. Nitrogen output requires a complete 24-hour urine collection, the collection of 3 consecutive complete 24-hr-urine samples is preferred, because intra-subject variation in urinary nitrogen excretion can be large (Gibson,1990). Normally, adults are in nitrogen balance. Positive nitrogen balance occurs during growth, pregnancy, athletic training and recovery from illness. A negative nitrogen balance happens when protein breakdown exceeds protein formation and can arise from conditions such as trauma, infection, sepsis, burns or surgery (Gibson, 1990; Konstantinides, 1992). Nitrogen balance requires the determination of total urinary nitrogen. This can be accomplished either by the use of the traditional Kjeldahl technique, which is laborious, time consuming, and is not routinely used in clinical laboratories, or by the determination

of urinary urea nitrogen as an estimate for total urinary nitrogen (Konstantinides, 1991). In unstressed persons, more than 80% to 90% of the total urinary nitrogen in the urine is excreted as urea (Gibson, 1990, Konstantinides, 1992). A correction factor for non-urea nitrogen compounds such as creatinine nitrogen, ammonia nitrogen, uric acid nitrogen and other minor nitrogenous compounds which are thought to remain stable on a general diet, is added to urinary urea nitrogen (Allison and Bird, 1964). Other miscellaneous nitrogen losses, which are seldom directly measured (stool, skin, expired air, saliva, blood) and may vary depending on the disease state, are accounted for by the addition of another correction factor. Thus the equation nitrogen balance = protein intake (g/day)/6.25 - [urinary urea nitrogen (g) + correction factor for non-urea nitrogen (g) + correction factor for miscellaneous losses (g)].

The debate of whether urinary urea nitrogen is sensitive enough to estimate total urinary nitrogen in highly stressed persons is ongoing.

1.7.1 Relationship between total urinary nitrogen and urinary urea nitrogen

A strong relationship between measured total urinary nitrogen and measured urinary urea nitrogen was observed in 81 patients for 564 study days with a variety of clinical and nutritional conditions (Blackburn, 1977). Linear regression between urinary urea nitrogen and total urea nitrogen showed a strong correlation ($r=0.98$, $p<0.001$). The difference between total urinary nitrogen and urinary urea nitrogen averaged 1.8±0.9 g nitrogen/day (mean±SD) and ranged from 0 to 5.8 g/day. These results formed the basis for a 2correction factor of 2g of nitrogen/day for the non-urea nitrogen compounds of the urine

in the nitrogen balance equation. Supporting evidence for the use of urinary urea nitrogen to predict total urea nitrogen comes from another study (Milner, 1993). Two hundred random 24-hour urine collections from 45 thermally injured patients were analyzed for total urea nitrogen and urinary urea nitrogen. Regression analysis showed a strong linear relationship between measured total urea nitrogen and predicted total urea nitrogen (urinary urea nitrogen x 1.25) ($r=0.936;p<0.001$). Regression analysis comparing nitrogen balance calculated from total urea nitrogen with that calculated from urinary urea nitrogen as expected also revealed a strong linear relationship ($r=0.98;p<0.001$). The ratio of urinary urea nitrogen/total urea nitrogen was 0.77 ± 0.10, slightly lower than the normally assumed proportion of 0.80 to 0.90 in unstressed persons (Gibson, 1990).

Konstantinides (1991), assessed the validity of estimating total urea nitrogen from measured urinary urea nitrogen in 315 nitrogen balance studies involving surgical, trauma, and critically ill patients. Although the overall ratio of urinary urea nitrogen/total urea nitrogen fell within the accepted value of $80\pm12\%$, the variability ranged from 12 to 112%, suggesting that in certain clinical situations, a correction factor is not appropriate to account for non-urea nitrogen components in urine and total urea nitrogen rather than urinary urea nitrogen should be measured for nitrogen balance. Loder (1989) examined the relationship between measured total urea nitrogen and measured urinary urea nitrogen in 34 patients admitted to hospital with a variety of conditions. Ten patients were admitted for elective surgery and a difference of 3.9 g of nitrogen was observed between the two methods. Thirteen patients underwent major surgery and received total parenteral nutrition and the observed difference between the two methods was 16.8 g nitrogen. The

last group consisted of 11 critically ill patients receiving enteral nutrition and the difference between total urea nitrogen and urinary urea nitrogen was 10.7 g of nitrogen. The inconsistency seen with enteral and parenteral nutrition is not unusual, since increased excretion of urea occurs and urinary urea nitrogen is no longer a valid index of total urea nitrogen (Gibson, 1990).

1.7.2 Other nitrogen losses

Faecal nitrogen losses in hospitalized patients receiving approximately 40 g of protein/day orally measured 1.2±0.8g of nitrogen, whereas patients receiving approximately 100g of protein/day faecal nitrogen measured 1.5-1.7g (Mackenzie,1985). When faecal nitrogen loss is not directly measured, and patients are consuming a mixed hospital diet, a nitrogen loss of 1.5g is usually assumed and used in the equation.

Calloway (1971a, 1971b) in a number of experiments with young healthy males determined many of the seldom measured nitrogen losses. Dermal nitrogen losses ranged from 168 to 246 mg per day. Another seldom mentioned loss of nitrogen is blood. Blood samples are routinely taken from hospitalized patients and will account for some loss. Blood contains 32 mg nitrogen/gram and the nitrogen loss in a single 10-ml sample can be twice the normal daily dermal nitrogen loss (336 to 492 mg/day). Another source of nitrogen loss which might be trivial in healthy persons, but could contribute to overall losses in COPD patients is that of sputum. The sputum of chronic bronchitics can cause a loss of up to one gram of nitrogen daily (Allison and Bird, 1964). To my knowledge, this has never been investigated. Ammonia, a regular constituent of expired air will also

lead to nitrogen losses. Calloway reported that with a ventilation rate of about 7 to 8 litres per minute, the daily pulmonary loss is about 80 ml of ammonia, containing 50 mg nitrogen.

1.7.3 Nitrogen balance studies in COPD patients

The nitrogen and energy relationships were examined during 2 weeks of enteral or total parenteral nutritional therapy in stable, malnourished patients with emphysema (Goldstein et al, 1988). Six malnourished patients requiring total parenteral nutrition but without lung disease were studied as a control group. Energy intake in the emphysema group was significantly lower (1.5 X measured REE) than in the control group (1.6 X measured REE, $p<0.05$). Protein intake was approximately 1.8 g/kg·day for the emphysema group, and was significantly higher than for the control group (1.5 g/kg·day, $p<0.05$). Energy and nitrogen balances were similar between the study groups and positive. As long as energy intake is appropriate for energy expenditure and sufficient protein is given to stable, malnourished individuals with emphysema, positive nitrogen balances can be achieved.

On the basis of the available data, an estimate of 2 g of nitrogen/day or a correction factor of 1.25 x urinary urea nitrogen is commonly used for the non-urea nitrogen components of the urine. Another 1.5 g of nitrogen for faecal losses and 0.5 g for dermal and miscellaneous losses are added when urinary urea nitrogen is used to calculate nitrogen balance. This equation may not be appropriate in certain conditions and

measured total urea nitrogen is preferable.

Balance studies provide a simple and rapid method to follow the changes in lean body mass during disease or nutritional therapy in hospitalized patients. However, care must be taken in the collection of complete 24-hour urine samples as well as in the accurate determination of protein intake.

PART TWO STUDY

2.1 Rationale of study

The clinical deterioration and diminished life expectancy (Cooper, 1994) that is associated with weight loss in a great number of patients with COPD has been recognized for many years. COPD patients are at risk of malnutrition and the importance of maintaining adequate body weight throughout life is important but is often difficult to accomplish when an underlying disease is present. In addition, some COPD patients are frequently hospitalized, and like other acutely ill patients providing optimal nutritional support is important during periods of high stress. Up to now feeding trials in COPD have focused on the rehabilitation of already malnourished subjects rather than the prevention of weight loss or malnutrition. The purpose of this study was to evaluate nutritional support during an exacerbation in hospitalized patients.

2.2 Hypothesis

The hypothesis of the study was as follows: aggressive nutritional support provided during an acute exacerbation of COPD will lead to improved health status.

2.3 Study design

The study was a randomized clinical trial to compare aggressive oral nutritional support with traditional hospital feeding procedures provided to COPD patients hospitalized with an exacerbation of their condition at the Montreal Chest Institute.

2.4 Objective of study

The principal objective of the study was to prevent loss of lean body mass during hospitalization, and to determine whether aggressive oral nutritional support would lead to improved respiratory and peripheral muscle strength, improved pulmonary function, reduced hospital stay, a greater distance walked in 6 minutes, and improved quality of life compared with those receiving traditional care.

2.5 Study population

Between November 1993 and June 1994, consecutive patients, aged forty to eighty-five, admitted to the Montreal Chest Institute with a diagnosis of COPD, and a forced expiratory volume in one second (FEV_1) that was equal or less than sixty percent of the predicted value were evaluated. Patients who required mechanical ventilation, had a non-intact gastrointestinal tract, had active cancer or other conditions predisposing to weight loss, were terminally ill, were unable to communicate in English or French, suffered from mental confusion or followed a special diet, were deemed ineligible. The purpose and the required adherence to our study protocol were explained to eligible patients, and informed, signed consent was obtained from 25 participants. The study was approved by the ethics committee of the Montreal Chest Institute.

2.6 Measurements

Baseline measurements including age, sex, anthropometry, pulmonary function, respiratory and peripheral muscle strength, level of dyspnea, and perception of general well-being

were collected as soon as possible after admission. Values of albumin, haemoglobin, hematocrit, leucocyte count, glucose and glucocorticosteroid doses were obtained from patients charts. Nitrogen balance studies were carried out on a subset of subjects. On day 14 of the study, measurements of body weight, pulmonary function tests, respiratory and peripheral strength tests, level of dyspnea as well as perception of general well-being were repeated to provide data on change over this period of time. Patients who were discharged before day 14, returned to the hospital for outcome measures. Pulmonary function, respiratory and peripheral muscle strength measurements were performed by the pulmonary lab at the Montreal Chest Institute. None of the laboratory technicians taking the measurements was aware of which subjects were in the treatment group. Level of dyspnea, and perception of general well-being were evaluated by the research dietitian, who was also responsible for the assessment of daily nutrient intake.

2.7 Randomization procedure

Randomization was carried out by the use of a random number table. A starting point was chosen from the table and the next thirty-one numbers were taken. Blocks of varying block size from four to six were used, and an even number was assigned to the treatment group, while an uneven number was assigned to the control group. Opaque, sealed envelopes numbered 1 to 32 were prepared. Each envelope contained a piece of paper with either a T for treatment group or a C for control group. After a subject consented to participate, the research dietitian opened the corresponding numbered envelope to discover the group assignment. All envelopes were kept and accounted for at the end of

the study.

2.8 Anthropometric measurements

Measurements of height and weight were recorded without shoes and with patients dressed in hospital gowns on a beam balance scale (Detecto Scales Inc Brooklyn, NY, USA). These measurements were then used to determine body mass index (BMI = kg/m^2). A subject was considered underweight if his or her body mass index was below 20. A body mass index between 20 and 27 was the range considered to have the lowest risk of illness for elderly people (Cornoni-Huntley, 1991). Overweight was defined as a body mass index greater than 27.

Triceps skinfold measurements (TSF) were made using Holtain skinfold callipers at the midpoint between the acromion process on the shoulder blade and olecranon process of the ulna. The mean of three measurements from the dominant arm was used. The midpoint obtained for the triceps skinfold was used as the level for the measurement of midarm circumference. With subjects standing, the metal tape was positioned perpendicular to the long axis of the arm and the circumference recorded.

2.9 Peripheral muscle strength

Handgrip strength, a well established measure of upper body strength and activities of daily living has been studied in older adults (Bassey and Harries, 1993). A handgrip dynamometer (Jamar Dynamometer; Alimed Inc Dedham, Mass) was used to measure isometric grasp in the dominant hand with the patient sitting, the shoulder adducted and

neutrally rotated, elbow flexed to 90 degrees, forearm and wrist in neutral positions. The mean of three measurements was recorded.

2.10 Pulmonary function tests

The forced vital capacity (FVC) is that volume of gas that can be expired as forcefully and rapidly as possible after maximal inspiration (Ruppel, 1994), and forced expiratory volume measured at one second (FEV_1), which is the volume of gas expired over the first second during the performance of FVC, were measured using the 570 Wedge Spirometer (Med Science Electronics, St.Louis, Missouri). The best of three measurements was recorded. Measurements were carried out according to standards of the American Thoracic Society (1991).

2.11 Respiratory muscle strength

Using a handheld manometer, inspiratory muscle strength (PI_{max}) was measured as the maximal static inspiratory pressure at the mouth at the end of a maximal expiration. Expiratory muscle strength (PE_{max}) was measured as the maximal expiratory pressure at the mouth after a maximai inspiration. The best of three measurements was recorded.

2.12 Dyspnea score

A sensation of breathlessness is often reported by patients with COPD and is related to the force of inspiratory muscle contraction. The quantification of dyspnea is important in the overall assessment of COPD. The oxygen-cost diagram was used, where everyday

activities are placed proportional to their oxygen cost along a 100 mm vertical line. The distance from the bottom of the scale to the patient's mark is measured, and it represents an index of the subject's dyspnea (McGavin, 1978).

2.13 General well-being questionnaire

A general well-being schedule (Dupuy, 1977) containing broad-ranging indicators of subjective feelings of psychological well-being and distress was administered at baseline and again at the end of the study. It is recommended as a tool where an indicator of subjective well-being is required. The self-administered questionnaire assesses how an individual feels about his "inner personal state", rather than conditions such as income, work, environment etc. The questionnaire covers both positive and negative feelings. Scores between 0 and 60 reflect "severe distress", scores between 61 and 71 "moderate distress", while scores between 73 and 110 represent "positive well-being".

Anxiety, depression, and general health were assessed using subscores of questions relating to these topics. A lower score reflecting a greater degree of anxiety, depression or poor general health.

2.14 Length of stay in hospital

Length of stay in hospital was recorded. It is an important outcome variable and of particular interest to physicians and hospital administrators, but because of the non-normal distribution of length of stay and the wide variability, the sample size of 32 is unlikely to be sufficient unless large differences are found. The length of stay for patients who

die during the study period, and those with an extremely long period of hospitalization will not be used, but an arbitrary value for length of stay will be calculated by using the mean hospital stay of the study population plus 2 standard deviations.

2.15 Nitrogen balance study

An attempt to obtain urine collections on all subjects was not successful, consequently, twenty-four hour urine collections for a subset were carried out. Urinary urea nitrogen was measured according to standardized procedures at the Royal Victoria Hospital. Total urinary nitrogen was estimated by adding correction factors of 2 g nitrogen for non-urea nitrogen components and an additional 2 g nitrogen for dermal and faecal losses. Using the relationship of protein intake (g)/6.25 - [(urinary urea nitrogen (g) + 4)] nitrogen balance data were obtained.

2.16 Glucocorticosteroid intake during study

Glucocorticosteroid intake was calculated from admission up to and including the study period of 14 days. Because of the difference in activity of the glucocorticoids, all medication (Solucortef, prednisone, solumedrol) was converted to an equivalent anti-inflammatory dose of methylprednisolone (Gilman and Goodman, 1985).

2.17 Dietary intake

Patients were randomized to either a supplemental or usual feeding group during hospitalization after baseline testing was performed. Subjects receiving supplemental

feeding were encouraged to eat at least 1.5 x REE if their body mass index was normal, (20-27) and if they were considered underweight with a body mass index of <20, their daily caloric intake was augmented to contain at least 1.7 x REE. The Harris and Benedict equation was used to establish resting energy expenditure. Subjects in both groups ordered their food and beverages from the hospital menu. In addition to the hospital tray, patients in the supplemental feeding group received oral supplements (Ensure, Ensure Plus, or a variety of puddings) or extra snacks to assure the required caloric intake was maintained. The type and amount of food and beverages consumed by subjects while in hospital were recorded by hospital personnel using a calorie count, and those results were verified by the research dietitian with 24-hour recalls at least every other day. If a subject was discharged prior to 14 days, 24-hour recalls were administered over the telephone. Nutrient analysis of food intake was completed with the Food Processor nutrient analysis program. Mean energy and macronutrient intakes were recorded.

2.18 Six minute walk

The 6 minute walk test measures the distance covered in 6 minutes and was administered only at the end of the study because subjects were considered unstable on admission to hospital and unable to walk the distance.

2.19 Statistical analysis

The analysis of the equivalency of the trial groups was evaluated by comparing the

similarity of the baseline characteristics of the two study groups using independent Student's t-test. Due to the loss of subjects either to death or follow-up, complete data versus incomplete data were compared using independent t-test. To determine changes within each group over the study period, paired t-tests were utilized. Changes in variables of interest (final-baseline) between the two groups, were analyzed using independent Student's t-test. In a further observational evaluation of changes in nutritional status Pearson's coefficient of correlation was used to describe the relationship between variables.

2.20 Sample size

Sample size was calculated for a clinically significant change in handgrip strength. A difference of less than 4 kg was considered of doubtful clinical importance. From a previous observational study, the standard deviation of the change in handgrip strength was 3.8 kg. A total sample size of 30 with Type I error of 0.05 and Type II error at .20 was thus required.

3 RESULTS

3.1 Study population

Between November 1993 and June 1994, ninety-five patients were admitted to the Montreal Chest Institute with a diagnosis of COPD. (Figure 1)

Forty-five patients had the following medical problems making them ineligible for our study. Two were diagnosed with coronary artery disease and heart failure, 10 had cancer, 9 were unable to communicate in English or French, 5 had psychological problems making it impossible for them to understand the purpose of the study, 2 required enteral nutrition, 2 were suspected of having a bowel obstruction, 3 wanted to lose weight, and 11 had physician prescribed diets, of which 5 were reducing diets and 6 required special diabetic diets. Fifty patients were eligible, of which 25 refused. Randomization of the 25 consenting subjects resulted in 12 in the control group and 13 in the treatment group. The final analysis consisted of complete data for six subjects in the control group and ten subjects in the treatment group. Data were considered complete if either

a) all baseline and outcome measurements were available or

b) if baseline, outcome or both measurements were missing for dyspnea score, general well-being questionnaire, handgrip strength, and 6 minute walk at the end of the study.

3.1.1 Control group

There was one error whereby a patient with a baseline FEV_1 %predicted of >60% was initially included but data could not be used in the analysis. Three patients refused to

come back for final outcome measures; their initial measurements were included in baseline analysis but they were considered as incomplete subjects. Two patients became too ill to undergo outcome measures, one of these patients died one day after study was completed, while the other patient remained in hospital for 93 days. Their data were used for baseline analysis only.

3.1.2 Treatment group

After randomization, one patient refused to continue and no data were available for analysis. One patient died on the 10th day of the study. Initial measurements were used in baseline analysis but the subject was considered as incomplete. One patient could not be contacted and did not return for outcome measures after leaving hospital.

3.2 Baseline data

The characteristics of the study population are summarized in table 4, and all variables, except age, were normally distributed. Baseline characteristics were similar between control and treatment subjects. The subjects participating in this study were severely obstructed with a FEV_1 % predicted of 30% for the control group and 31% for the treatment group. The exacerbation of their disease was reflected in their dyspnea and general well-being scores. The control group had a baseline dyspnea score of 35 (mm), while the treatment group's score was 36 (mm). Both groups experienced breathlessness while standing up or walking on a flat surface. There were no significant differences in total general well-being scores and subscores for anxiety, depression and general health

between the groups. Both groups were anxious and depressed, and perceived their general health to be poor on admission to hospital.

More males (n=15) than females (n=8) entered the study reflecting the greater prevalence of this disease among men.

3.2.1 Biochemical indices of study population

Laboratory results of routine blood tests were not available for the entire study population, and are summarized in table 5. Albumin, hematocrit and haemoglobin concentrations were within reference ranges (Tilkian, 1987) and were similar between the groups. Total leucocyte count and glucose levels were elevated in both the control and treatment group but not different between the groups.

3.3 Complete data versus incomplete data

As was illustrated in Figure 1, six subjects in the control group and 10 subjects in the treatment group completed the trial. Since seven subjects did not complete the study, an analysis (independent t-test) of baseline characteristics between subjects who completed the study and those who did not was carried out, to evaluate any differences between the groups. The results are summarized in tables 6 and 7.

Half the women (4 of 8 or 50%) did not complete the study, while only 3 of the men (or 20%) did not complete the study. This is reflected in the significantly lower body weight recorded for the incomplete group (54.58 kg versus 68.35 kg). The handgrip strength in the incomplete group was also significantly lower (21.95 kg vs 31.14 kg) which reflects

the higher proportion of women in the incomplete group. The incomplete subjects were significantly more depressed than tne completed subjects (16.18 points versus 10.25 points); depression may have been a reason for dropout.

The energy and macronutrient intake, summarized in table 7 for subjects not completing the study was significantly lower (1,433 kcal) than that for subjects completing the study (2,304 kcal).

3.4 RESULTS OF CLINICAL TRIAL

3.4.1 Baseline characteristics

Since no differences, apart from the above mentioned variables existed between the completed and incomplete subjects, changes in outcome measures among completed subjects were analyzed. Also paired t-test was used to analyze changes within the groups over the 14 day study period. Baseline characteristics and changes for completed subjects are summarized in table 8.

Baseline characteristics were similar between the study groups. Body mass index values were used to define underweight, normal weight and overweight. Two subjects were underweight with a body mass index of less than 20, seven had normal weight with a body mass index between 20 and 27, while seven were overweight with a body mass index greater than 27.

3.4.2 Lung function

Both groups were severely obstructed on admission to hospital. Baseline FEV_1 % predicted was 34% in the control group and 29% in the treatment group. No significant difference in the change in FEV_1 % predicted over the study period between the two study groups was observed. In addition, no changes in FEV_1 % predicted within the study groups occurred over the 14 days of the study.

FVC % predicted on admission to hospital was not statistically different in the two study groups, however, the treatment group had a FVC of 58% predicted, while the control group's value was 73% predicted, (p=0.084). This difference is sufficiently large to be potentially of clinical importance. A significant difference in the change in FVC % predicted during the study between the treatment group (+11%) and the control group (-4%), (p=0.026) was observed. While the FVC % predicted did not significantly change in the control group during the trial, the improvement seen in the treatment group (+11%) was significant (p=0.0403).

3.4.3 Respiratory and peripheral muscle strength

Both maximal inspiratory and expiratory muscle strength were not significantly different between the study groups on hospital admission. No significant changes occurred within each group nor were there any differences in the changes of PI_{max} and PE_{max} between the control and treatment groups during the study period.

Grip strength was similar in the two groups on admission, and were comparable to values obtained in healthy men and women over the age of 65 years in England (Bassey, 1993).

No significant changes in grip strength occurred within each group nor was there any significant difference in change in grip strength over the study period between the two groups observed.

3.4.4 Dyspnea score

Both control group and treatment group experienced breathlessness while standing or walking on a flat surface on admission to hospital. No significant difference in change of dyspnea score was observed during the study period between the groups.

3.4.5 General well-being

On admission to hospital, the general well-being score of both groups was low and not statistically significantly different, but the control group felt severe distress (48 points), whereas the treatment group experienced moderate distress (69 points). Anxiety, depression, and general health were similar between the groups. The total general well-being score in both groups tended to improve over the study period but the change was not statistically significant.

3.4.6 Six minute walk test

At the end of the study, the treatment group was able to walk further (262 m) than the control group (171 m), but the difference was not statistically significant.

3.4.7 Days in hospital

The number of days (range) spent in hospital was similar between the control group (5 - 17 days) and the treatment group (9 - 33 days), p=0.084.

3.4.8 Energy and macronutrient intake

The energy intakes of the two groups are summarized in table 9. The treatment group was able to ingest significantly more calories (2,516 kcal) than the control group (1,951 kcal, p=0.012) without reporting any side effects such as increased breathlessness or gastrointestinal discomfort. The ratio of energy intake/Harris Benedict equation resulted in a ratio of 1.88 for the treatment group, significantly higher than the control group's ratio of 1.43, p=0.008.

Carbohydrate intake was significantly higher in the treatment group (312g) than in the control group (246g), p=0.021. Fat intake was also significantly higher in the treatment group (102g) compared with the control group (77g), p=0.020. The difference in protein intake approached significance, with an intake of 99g in the treatment group and 80g in the control group, p=0.059.

3.4.9 Biochemical indices of nutritional status

The mean albumin, hematocrit, and haemoglobin concentrations were similar between the study groups and were within normal reference values (Tilkian, 1987). The total leucocyte count was similar between the groups, and the results for the control group fell just within the normal reference range, while the concentration for the treatment group

was elevated. Glucose values were elevated in both groups but not significantly different between the groups.

Results for glucocorticosteroid intake are summarized in table 10, and as expected both groups had similar intakes.

3.4.10 Nitrogen balance studies

Nitrogen balance studies were carried out for four subjects in the control group and six subjects in the treatment group. The result of one control subject was discarded because of a very low total urine volume. The remaining three control subjects and six treatment subjects were in negative nitrogen balance, and their combined results are summarized in table 11 and figure 8. The mean loss of nitrogen was -8.42±1.74 g nitrogen/day.

4. INTERRELATIONSHIPS BETWEEN CHANGES IN WEIGHT, GENERAL WELL-BEING, NITROGEN BALANCE, STEROID INTAKE AND FUNCTIONAL STATUS.

Although no cause and effect can be inferred from correlation analysis, an evaluation of the variables of interest without regard to treatment status is worthwhile. The observational assessment can often shed light on the usefulness of measurements for future studies. Correlation analyses were performed on combined data from control and treatment subjects and are summarized in tables 12, 13, 14, and 15.

4.1 Relationship between changes in weight and changes in functional status

The expectation that improvement in body weight would result in a corresponding improvement in pulmonary function was borne out as the moderate correlation between change in FEV_1 (%predicted) and change in body weight approached significance (r=0.468, p=0.067). A good correlation was noted between change in FVC (%predicted) and change in body weight (r=0.520, p=0.039). No correlation between change in PI_{max}, PE_{max} and change in body weight was found. A strong positive correlation was found between change in body weight and change in grip strength (r=0.726, p=0.002).

4.2 Relationship between changes in general well-being and functional status

The general well-being questionnaire, assessing subjectively the well-being of an individual, showed a good positive correlation with change in dyspnea score (r=0.728, p=0.026). Although weak and not significant the negative correlation found between general well-being and number of days spent in hospital was not unexpected (r= -0.481, p=0.134). Also a weak positive correlation was seen between general well-being and distance walked at the end of the study (r=0.454, p=0.186).

4.3 Relationship between nitrogen balance and outcome measures

As can be seen from table 14, no correlation between nitrogen balance and change in weight, change in PI_{max}, PE_{max}, and change in grip strength was established.

4.4 Relationship between steroid intake and functional status

The well known catabolic effects of glucocorticosteroids and their relationship to peripheral and respiratory muscle strength are of interest to the clinician and nutritionist alike. As the results in table 15 indicate, good correlations between methylprednisolone intake during the study period and change in grip strength ($r = -0.755$, $p=0.001$), change in general well-being ($r = -0.654$, $p=0.029$), and nitrogen balance ($r=-0.731$, $p=0.025$) were noted. The weak and not significant negative correlation between methylprednisolone intake and pulmonary function, as well as change in weight are in the expected direction. No correlation between methylprednisolone intake and respiratory muscle function was noted.

5 DISCUSSION

The rational for our study was based on the fact that well-designed, randomized controlled trials providing nutritional support to already malnourished COPD patients have been successful and have resulted in significant improvements in weight and concomitant improvements in respiratory and peripheral muscle function. However, the prevention of loss of lean body mass in hospitalized COPD patients with an exacerbation of their disease has never been investigated. We were interested in preventing loss of lean body mass, as the prevention of weight loss could be more effective in terms of therapeutic benefits, and may also result in reduced health care costs. Refeeding already malnourished individuals is costly, and long term benefits have not been established. Also, in older aldults the regaining of lean body mass can be a challenging task. Our study is the first to report on the effect of nutritional therapy on changes in functional status during an acute exacerbation of COPD.

Lung function

A comparable degree of airflow obstruction (FEV_1 %predicted) was present in both groups upon admission and no change in FEV_1 (%predicted) occurred during hospital stay or with nutritional therapy. This is in keeping with successful nutritional intervention studies carried out in malnourished but stable COPD patients (Wilson et al, 1986, Efthimiou et al 1988, Whittaker et al, 1990, Knowles et al, 1988), where despite weight gain and improvements in respiratory muscle function, pulmonary function measures did not improve. FEV_1 is a measure of functional impairment (narrowed airways, decreased elastic recoil) and as such may not respond to nutritional therapy. Pre admission values

for FEV_1 (% predicted) were not available in our study, and it is unknown whether pulmonary function measurements had returned to pre-illness values. Fourteen of our 16 subjects were either normal weight or overweight and we did not really expect this measure to change. An interesting picture emerges when looking at that the individual changes of FEV_1 %predicted (figure 2); 5 of the treatment subjects improved, 3 remained the same, and 2 worsened. The picture for the control subjects is not as encouraging, with 2 subjects marginally improving, and 4 either deteriorating or remaining at admission levels. Although nutritional intervention cannot reverse the severe obstruction, it can give patients a sense of improved vitality which may influence their FEV_1 measurements.

The moderate correlation found between change in weight and change in FEV_1 might be the result of the patient's perception of improvement as they felt better and were ready to be discharged or already discharged from hospital.

Contrary to findings in successful refeeding studies (Wilson et al, 1986, Efthimiou et al 1988, Whittaker et al, 1990), FVC improved significantly in the treatment group (11.1%, p=0.040), while no such improvement was seen in the control group (-4.5%, p=0.089). These results should be interpreted with prudence since the treatment group was clinically worse off on admission to hospital, and a greater improvement prior to release from hospital would be anticipated. It is possible and plausible that the additional energy (565 kcal/d) and protein intake (19 g/d) would improve a person's sense of well-being and motivate the individual to generate more strength to forcefully move air out of the lungs. In addition it is important to stress the fact (figure 3) that none of the control subjects showed any improvements in FVC (% predicted) over the study period, whereas 6 of the

treatment subjects showed an improvement in FVC (%predicted), 1 individual's value deteriorated, and 3 remained essentially the same.

Respiratory and peripheral muscle strength.

No changes in PI_{max} and PE_{max} were noted over the study period in both groups (figures 4 and 5). Respiratory muscle strength evaluated as PI_{max} and PE_{max} is reduced in malnourished individuals (Arora and Rochester, 1982) but can be strengthened with short term nutritional therapy (Wilson et al, 1986, Whittaker et al, 1990, Rogers et al, 1992). The great variability in baseline muscle strength as well as the variable changes in PI_{max} and PE_{max} over the study period, make it difficult to interpret our findings. While stable, malnourished COPD patients may be a more homogeneous group, the severity of the exacerbation among patients admitted to hospital and their subsequent improvement will influence their maximal voluntary effort necessary for these measurements. The respiratory muscle strength measurements found in our study group were normal for individuals of similar ages.

Since all patients admitted to the Montreal Chest Institute were treated with steroids, the relationship between methylprednisolone intake and respiratory as well as peripheral muscle function were explored.

No correlation between methylprednisolone intake in hospital and respiratory muscle strength was found. This is similar to another study (Decramer, 1994) in which steroids administered during hospital stay did not affect muscle force, however their average daily dose calculated for the previous 6 months significantly ($p<0.05$) influenced PI_{max} but not PE_{max}. No attempt to calculate intake prior to hospitalization was made in our study.

Chronically active muscles, such as the respiratory muscles are thought to be less susceptible to steroid-induced myopathy than less active peripheral muscles such as would be involved in hand grip (Ferguson, 1990, Lieu et al, 1993). Our study corroborates these arguments, as no correlation between PI_{max} and PE_{max} was noted. Picado et al, 1990 did not find a relationship between steroid treatment and muscle force in asthmatics receiving low doses of steroids (13±4.4 mg/day) over a long period of time (9.7±3.8 years). A possible training effect of severe asthma on inspiratory and expiratory muscle function, which could have masked respiratory steroid myopathy has been suggested for the negative findings (Gallagher, 1994). Normal healthy men were studied by Wang (1991) who inferred that 20 mg prednisone/day for 2 weeks had no effect on respiratory muscle function in healthy adults. Their study group consisted of healthy young (19 - 39 years) males, whereas COPD patients are generally older and sick and therefore not comparable. The effects of steroids in healthy individuals are probably quite different from older patients with respiratory disease. The negative studies are by no means evidence that steroids have no effect on respiratory muscle function and further investigations are needed to clarify this issue.

Peripheral muscle strength

Grip strength (figure 6) did not change over the study period in either group. However, the correlation between methylprednisolone intake and change in grip strength, was good ($r=-0.755$, $p=0.001$). Decramer (1994) also demonstrated that weakness in quadriceps force was independently related to steroid intake in COPD and asthmatic patients. Because of the relative physical inactivity of peripheral muscles in hospital, disuse may

have indirectly contributed to the correlation, independent of methylprednisolone intake. Whether the very good correlation between methylprednisolone intake and change in grip strength exists because patients with lower grip strength or lower FEV_1, and FVC are more ill and receive higher doses of steroids, cannot be answered in this study because the small number of subjects is not suitable for multivariate analysis.

The recognized catabolic effects of steroids require further investigation as they may be responsible for loss of lean body mass but may also contribute to osteoporosis, infections, cataracts, and gastrointestinal bleeding (Saag et al, 1994).

Nutritional parameters.

Studies to date have established the prevalence of malnutrition, defined as <90% IBW between 23 and 43 percent. The 43% of malnourished COPD patients found in the study by Openbrier (1983) were exclusively subjects with emphysema, whose nutritional status is thought to be different (poorer) to those with chronic bronchitis (Openbrier, 1983, Wilson et al, 1989). Body mass index, another useful, albeit crude indicator of nutritional status demonstrated that 23% of COPD patients were underweight (Sahebjami, 1993). Only 2 patients in our study were considered underweight with a body mass index of <20. Since our study recruited patients as they were admitted to hospital with an exacerbation, and acknowledging the established relationship between decreased body weight and mortality (Wilson et al, 1989), it is possible that fewer underweight patients survive, and we simply did not meet as many in our study as others have who recruited stable outpatients from clinics or from chart reviews.

Body weight did not change in either group during the study, however the variability

among individuals was great (figure 7). Change in body weight as a measure of change in nutritional status in acute exacerbations of COPD is not very useful. Water balance is often disturbed. Fluid retention (in cor pulmonale) and changes in fluid balance as a result of steroid treatment or malnutrition can occur.

Energy and macronutrient intake

The purpose of the study was the prevention of weight loss and whether hospitalized COPD patients would benefit from nutritional support during an acute exacerbation of their disease. The additional intake by the treatment group (1.88 X REE) did not result in improvements in FEV_1 %predicted, respiratory and peripheral muscle strength, general well-being, and level of dyspnea. Given the adequate intake by the control group (1.43 X REE) and the fact that 14 out of 16 patients were normal weight or overweight, the lack of difference is not surprising. In another study at the same institution (Haddad, 1993), the mean energy and protein intakes in hospitalized COPD patients were lower, ranging from 1,300 to 1,600 kcal/day and 54 to 66 g protein/day. Although no attempt at influencing the control group's diet was made in our study, daily visits by the dietitian could have influenced the intake by the control group, resulting in higher than previously recorded intakes. The treatment groups intake of 1.88 X REE appears to be copious but should be regarded as an estimate only since the Harris Benedict equation, which was used to estimate energy expenditure, has been found to underestimate the needs of unstable, hospitalized COPD patients (Moore J., 1988). Also, successful refeeding trials in stable, malnourished COPD patients have resulted in intakes of at least 1.7 X REE (Rogers et al, 1992), 1.9 X REE (Efthimiou et al, 1988) and 2.2 X REE (Whittaker et al,

1990).

Nitrogen balance

Nitrogen balance is the most useful measure available to the dietitian to assess changes in body protein during nutritional therapy or disease. As attempts at collecting complete 24-hour urine in all subjects were unsuccessful, only 9 nitrogen balance studies were available, but they reveal a distressing picture as all 9 patients recorded negative nitrogen balances (figure 8). Erroneous false positive nitrogen balances, due to overestimation of protein intake and underestimation of nitrogen loss, are possible (Kopple, 1987).

In unstressed persons, more than 80 to 90% of the total urinary nitrogen in the urine is excreted as urea. However, some investigators (Konstantinides, 1991) caution against the use of urinary urea nitrogen to estimate total urea nitrogen as the variability among critically ill patients can be great. Others have reported good agreements between urinary urea nitrogen and total urea nitrogen in critically ill patients with a variety of clinical conditions (Blackburn, 1977, Milner, 1993). Most patients in our study recorded substantial negative balances, and one could speculate that had we been able to measure total urinary nitrogen plus all miscellaneous losses (faeces, blood, expired air, sputum, etc) our nitrogen balances might have been more negative than recorded.

A further investigation revealed a very good correlation between methylprednisolone intake and nitrogen balance ($r=-0.731$, $p=0.025$, $n=9$). This relationship was greatly influenced by one patient, whose steroid intake was the greatest (182 mg/d), and whose nitrogen balance was the most negative (-19 g N/day). When this patient's data were

removed, the correlation was no longer significant. It is however, important to point out this individual was not considered an outlier, and therefore left in the analysis. Also had we succeeded in calculating nitrogen balances for all 16 subjects, it is conceivable that more than one patient had nitrogen wasting of the magnitude recorded. Nitrogen balances were determined, on average, on the 6th day after being admitted to hospital, at which time steroid dosages were high, and recognizing their catabolic effects, the very negative nitrogen balances were not unexpected. A limitation to our study was that serial determination of nitrogen balance in the same subject, a good indicator of change in body protein, was not carried out. Thus we are left with the question of whether the negative nitrogen balances continued throughout the study period or would improvements have taken place either as a result of the additional nutritional support, the tapering off of steroid dosage or both.

Nitrogen wasting during treatment with high levels of glucocorticosteroids (1000 mg/day for 3 days) was clearly demonstrated in patients with rheumatoid arthritis (Roubenoff, 1990). Nitrogen loss which was negative during therapy (-5.77±1.30 g nitrogen/day) continued being negative after therapy had stopped (-3.54±1.38 g nitrogen/day) (mean±SEM) despite high energy (46.8±6.2 kcal/day) and protein (1.6±0.6 g/day) intakes. Whether this nitrogen loss can be prevented in COPD patients, whose energy requirements are already elevated, while in hospital with an exacerbation has not been established. Stable, malnourished patients with emphysema were able to gain nitrogen and achieve nitrogen equilibrium with energy intakes of 46.8±1.9 kcal/kg and 1.8±0.08 g protein/day (Goldstein et al, 1988). The energy requirements in our study were based

on measured REE from successful refeeding trials, and patients in the treatment group were able to ingest 38±3 kcal/kg and 1.5±0.11 g protein/kg. It was thought that patients admitted with an exacerbation would not be stable enough to have REE directly measured by indirect calorimetry.

It is feasible that energy and protein requirements are very high during an exacerbation. In the 9 individuals in whom nitrogen balances were performed, energy (32 kcal/kg·day) and protein (1.3 g/kg·day) intakes were insufficient for their needs.

The nitrogen wasting needs to be investigated because of the consequences that loss of lean body mass has on respiratory muscle strength (Rochester,1991), FEV_1 %predicted (Braun et al, 1984), exercise capacity (Gray-Donald, 1989, Schols, 1993) and mortality (Wilson, 1989). Keeping in mind, that the majority of patients with COPD are elderly, and we now know that with advancing age, more calories are needed to maintain body cell mass of malnourished patients, and a depleted body cell mass is more slowly restored in older patients (Shizgal, 1992), the determination of energy and protein requirements for COPD patients is crucial.

To put the findings of the nitrogen balance studies in perspective, it is useful to underline that a nitrogen loss of ~ 8.4g/day will result in a loss of ~ 53 g protein/day. Using the relationship that lean body tissue is 20% protein, an estimated loss of 263 g of lean tissue/day can develop if negative nitrogen balances are not corrected.

Quality of life.

Both groups experienced breathlessness while standing or walking on a flat surface on

admission to hospital. Although both groups' sensation of breathlessness improved over the study period, no significant change in level of dyspnea was reported in either group at the end of the study. This is in contrast to findings by Efthimiou (1988), whose malnourished, supplemented group reported significantly ($p<0.05$) higher scores after a 3 months supplementation period. The perception of breathlessness is likely to be worse on admission to hospital, as increased breathlessness is often the reason why patients are admitted. One would expect their own perception of dyspnea to be improved after 14 days but this was not the case. The level of dyspnea recorded in this study group can severely curtail simple tasks of daily living such as walking, dressing, light household activities, and the good correlation between change in general well-being and change in dyspnea ($r=0.728$, $p=0.026$) reflect the limitation COPD inflicts on its patients.

Length of hospital stay

Due to the small sample size, a comparison of length of stay in hospital between the groups is not helpful. Five of the 6 patients in the control group were discharged on day 15 or before, while only 1 remained longer than 15 days in hospital. Five individuals in the treatment group were also discharged on day 15 or earlier, however, 5 remained in hospital for more than 15 days. Treatment subjects were clinically more obstructed on admission as was evident by their FVC measurements, and this could have resulted in a prolonged hospital stay.

Power analysis.

An earlier observational study carried out at the Montreal Chest Institute formed the basis

for our sample size calculations. A total sample size of 30 (15 per group) with Type I error of 0.05 and Type II error at 0.20 was required to detect a clinically significant change in handgrip strength. Power calculations carried out in our study (table 16) would indicate that, for our originally hypothesized change of 4 kg in grip strength, we would have had sufficient power (Power >0.80) had we reached 24 completed subjects.

For PI_{max}, PE_{max}, dyspnea score, and distance walked in 6 minutes, our power was 0.28, 0.23, 0.14, and 0.56 respectively. To gain adequate power for these variables, taking into account the variability that existed in our population, and the clinically meaningful changes necessary, many more subjects needed to be recruited.

A sample size of 16 was adequate to detect changes in FVC %predicted (Power >0.90). It was almost sufficient to detect a clinically significant change of 10% for FEV_1 %predicted, however, we only found a non significant change of 5.46%.

The difficulty of recruiting acutely ill patients is evident by our small sample size (n=16) and our incomplete data (n=7). While other investigators (Wilson D. et al, 1986, Whittaker J. et al, 1990, Efthimiou J. et al, 1988) were successful in improving weight and respiratory muscle function in relative small samples of stable, malnourished COPD patients, the severity of an exacerbation among patients admitted to hospital varies widely, and will profoundly affect the statistical power of the investigation.

6 CONCLUSION

Our study clearly demonstrated that a significant increase in oral intake in patients hospitalized with an acute exacerbation is possible. Unfortunately, the additional intake did not result in improvements in FEV_1 %predicted, respiratory and peripheral muscle strength, general well-being, and level of dyspnea. Distance walked in 6 minutes at the end of the study was not different between the study groups.

Evidence from the negative nitrogen balances among hospitalized COPD patients underline the importance of proper nutritional assessment and intervention during hospitalization. The implications of prolonged and unchecked negative nitrogen balances are serious as loss of lean body mass is associated with poorer prognosis in individuals with COPD.

The catabolic process may have resulted from elevated energy requirements, inadequate intake or been induced by high doses of glucocorticosteroids.

Hospitalized COPD patients are highly stressed and catabolic; the means to preventing protein wasting during an acute exacerbation remains to be established.

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Study population

Figure 1

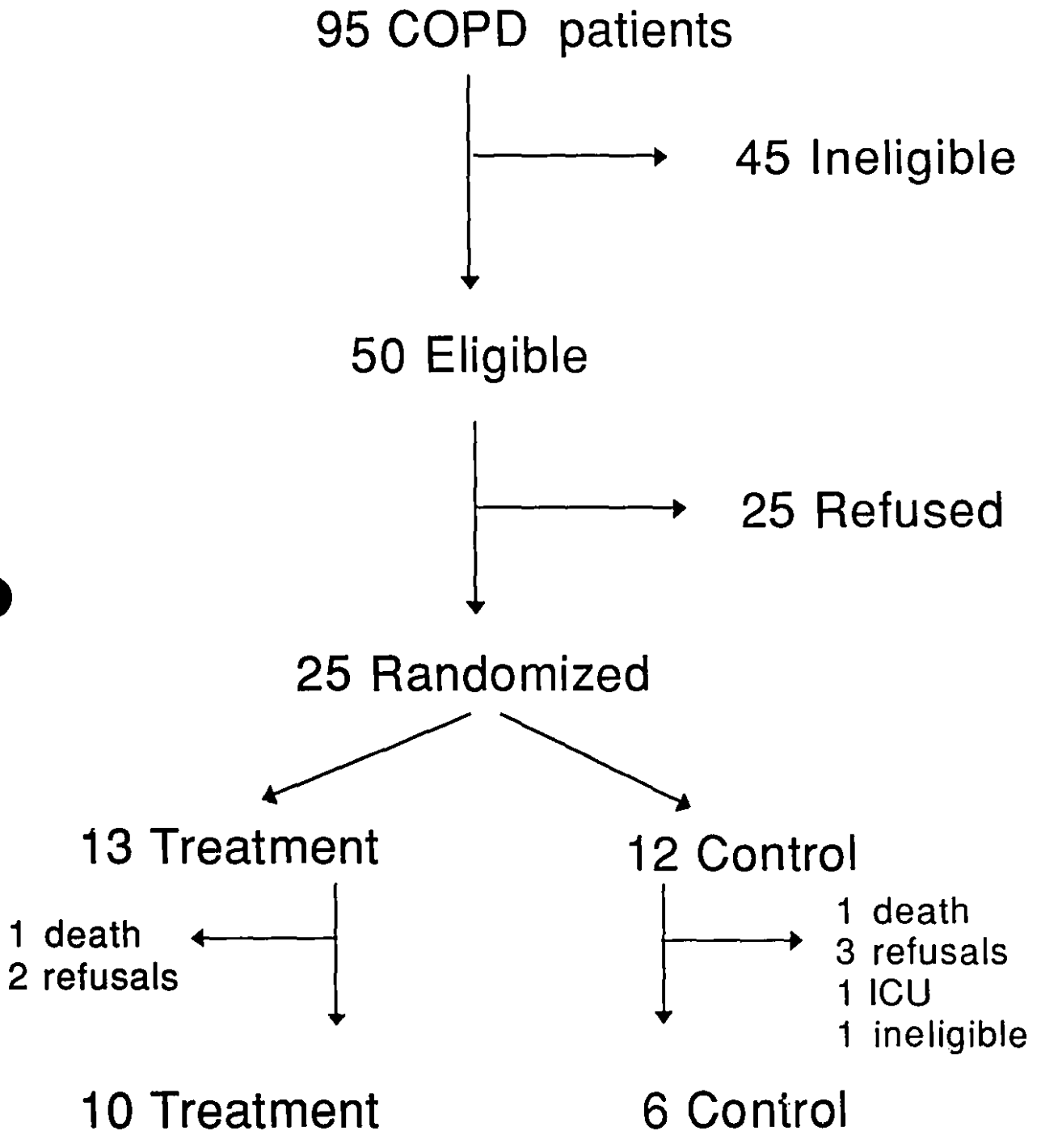

Figure 2

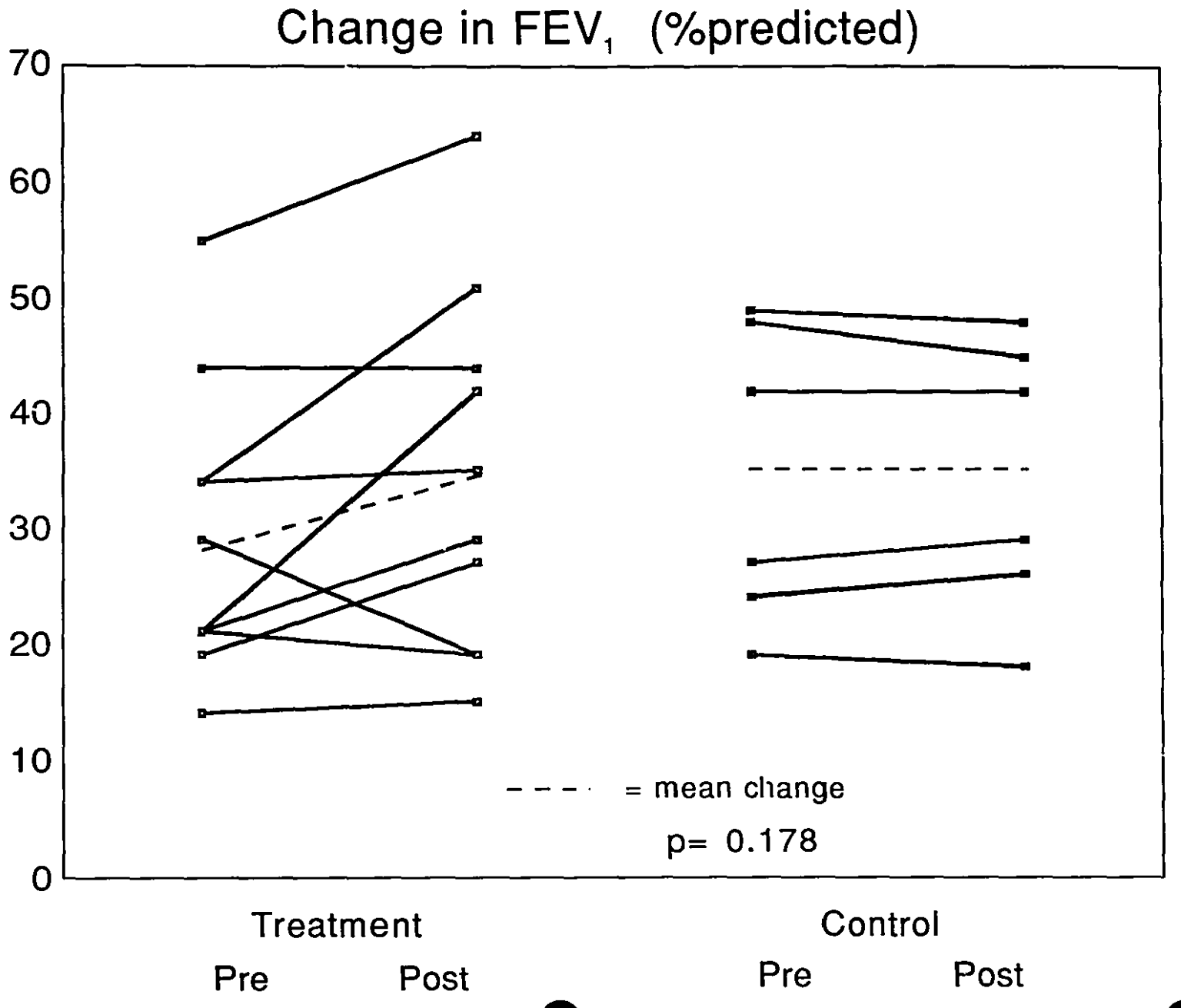
Change in FEV1 (%predicted)
70
60
50
40
30
20
10
0
= mean change
p= 0.178
Treatment
Pre
Post
Control
Pre
Post

Figure 3

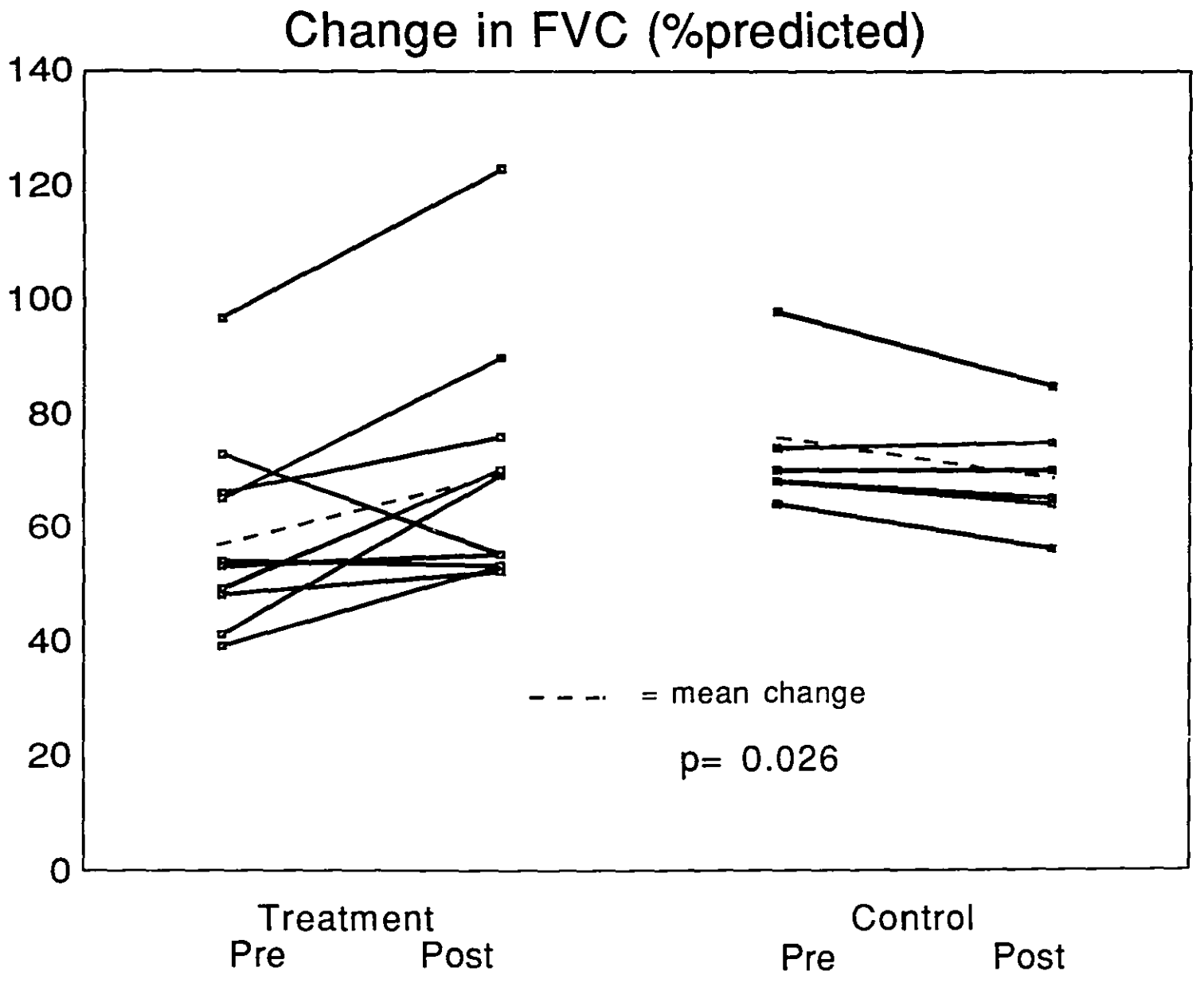
Change in FVC (%predicted)
140
120
100
80
60
40
20
0
= mean change
p= 0.026
Treatment
Pre
Post
Control
Pre
Post

Figure 4

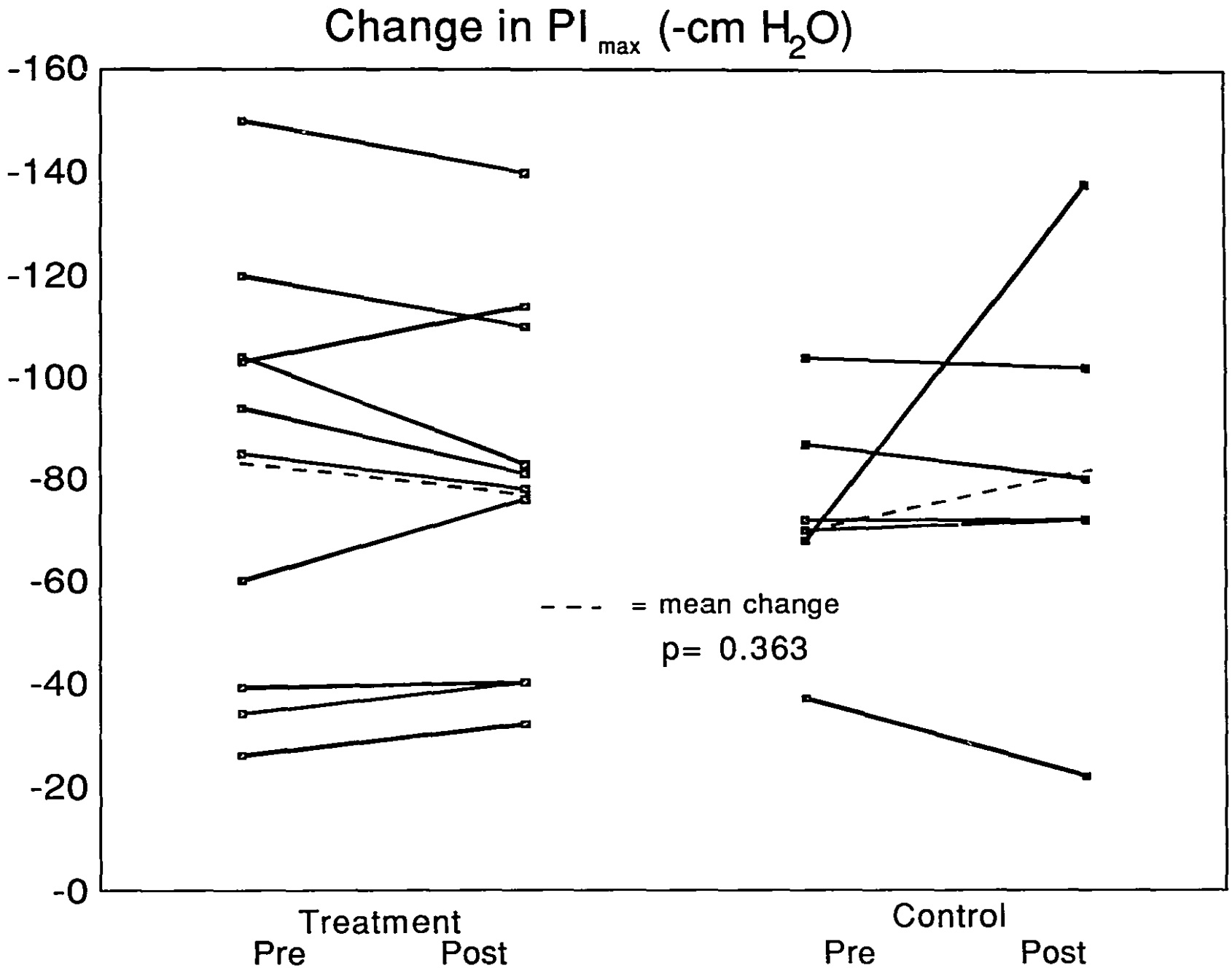
Change in PI_{max} (-cm H_2O)
-160
-140
-120
-100
-80
-60
-40
-20
-0
= mean change
p= 0.363
Treatment
Pre
Post
Control
Pre
Post

Figure 5

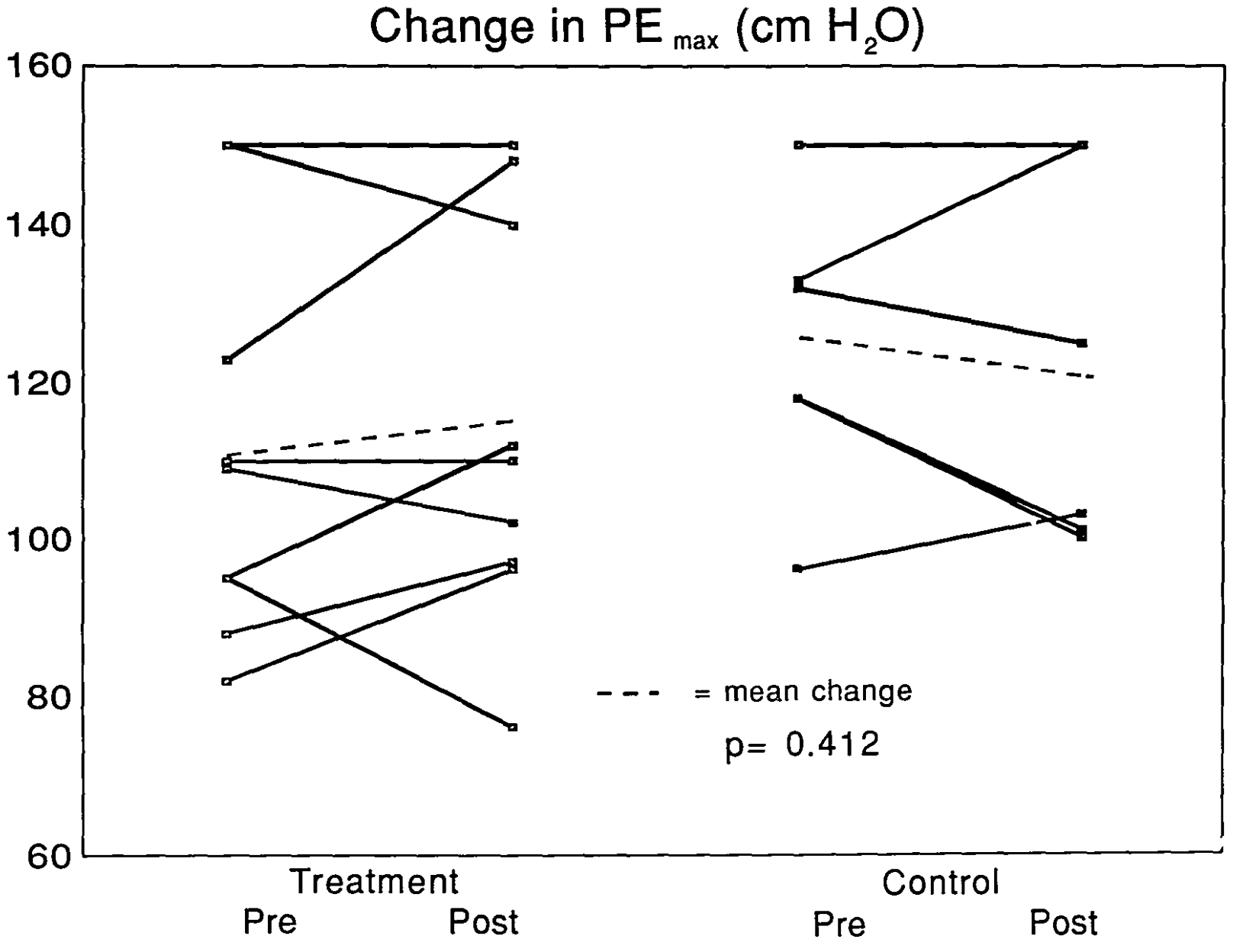
Change in PE max (cm H2O)
160
140
120
100
80
60
= mean change
p= 0.412
Treatment
Pre
Post
Control
Pre
Post

Figure 6

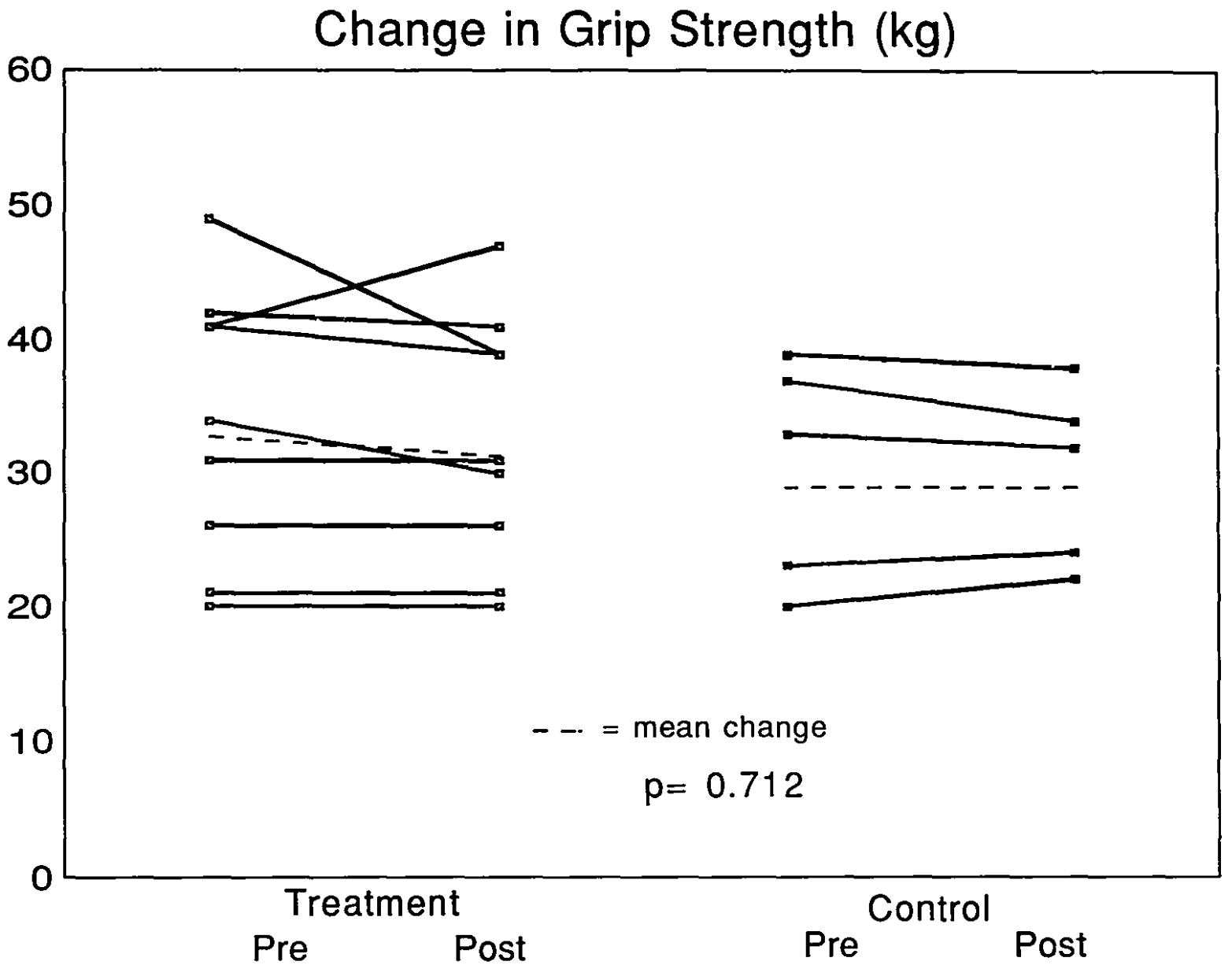
Change in Grip Strength (kg)
60
50
40
30
20
10
0
= mean change
p= 0.712
Treatment
Pre
Post
Control
Pre
Post

Figure 7

Changes in Body Weight

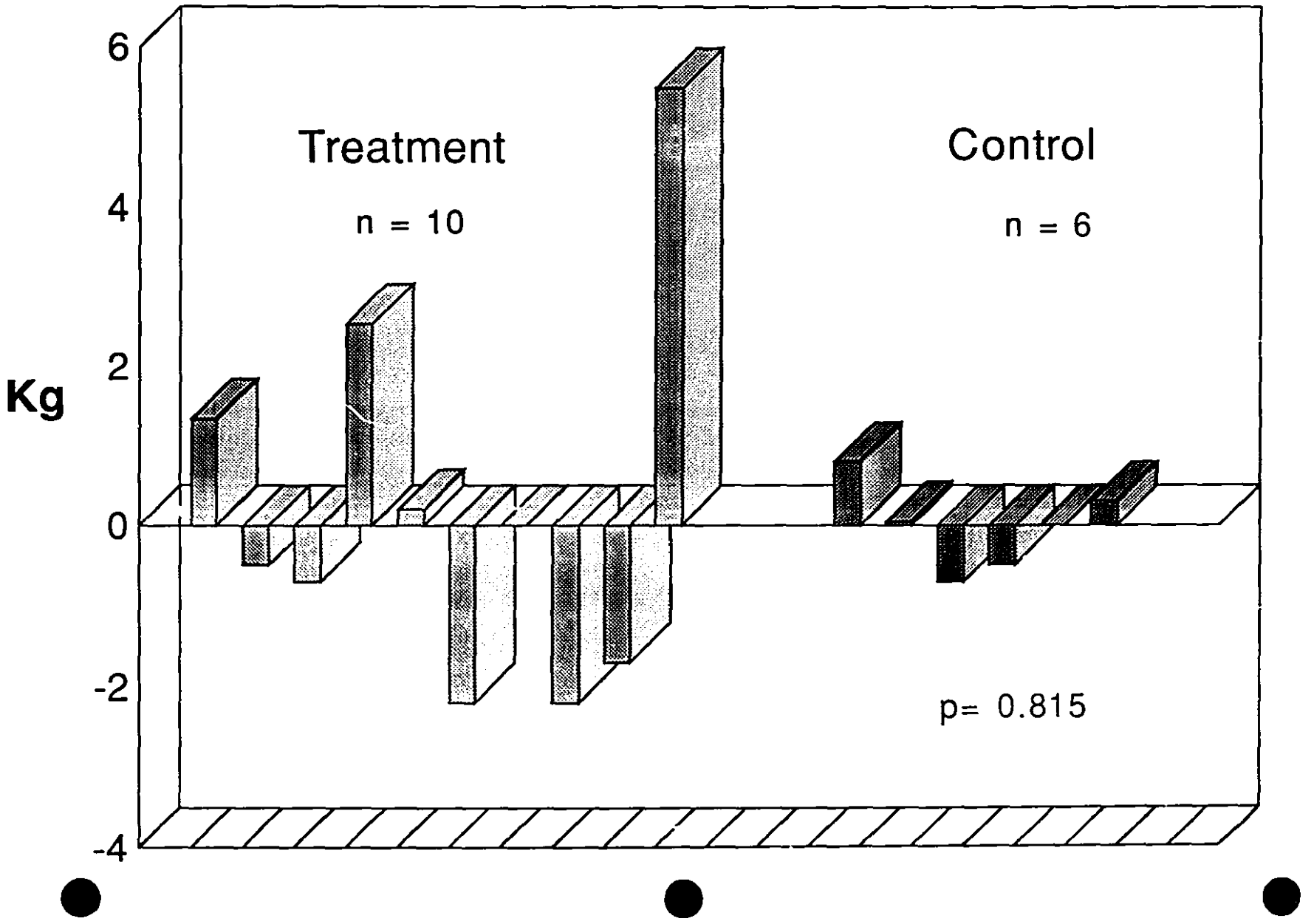

Figure 8

Nitrogen Balance

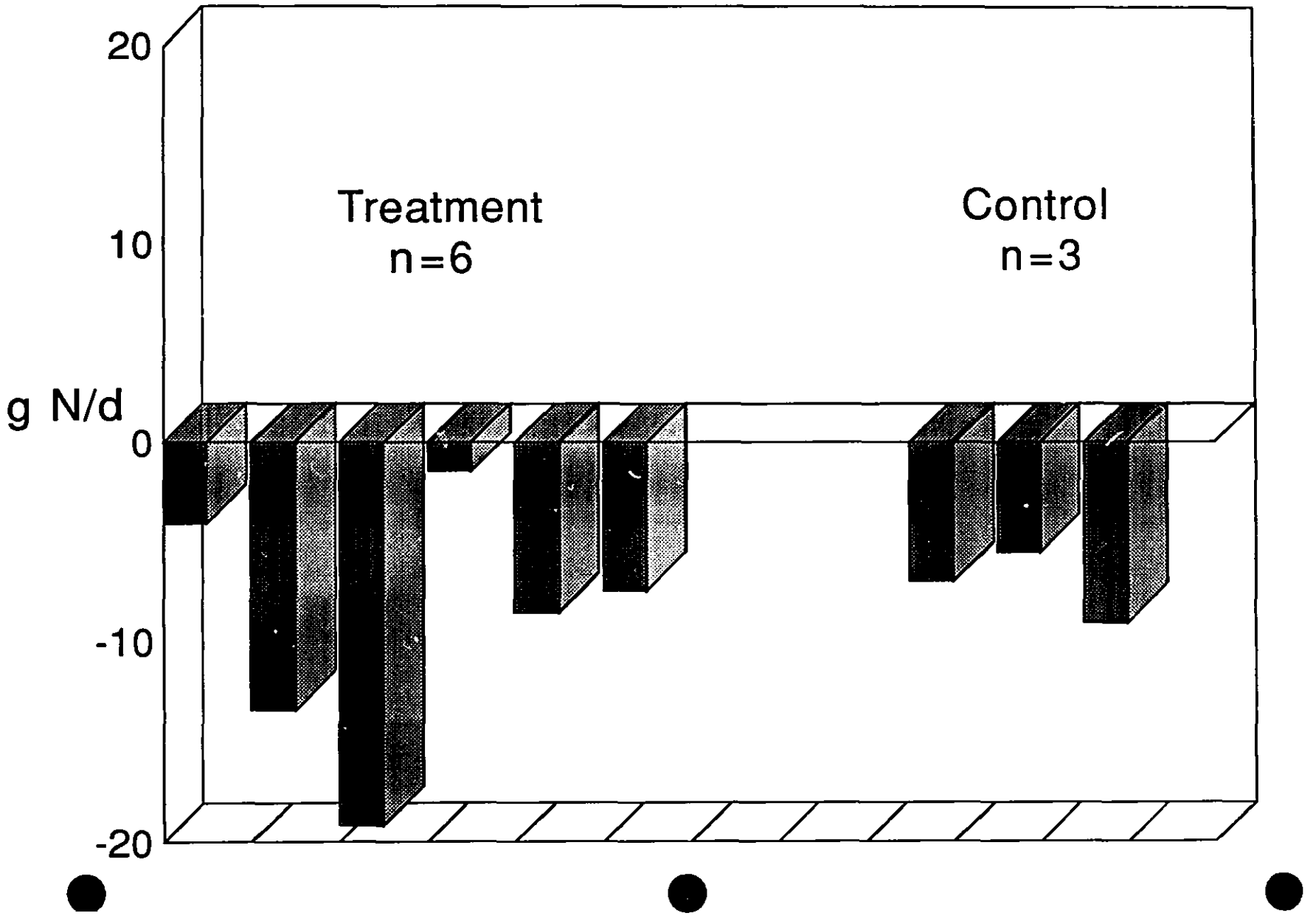

Table 1. Summary of studies determining the nutritional status of patients with COPD.

Author(s)	Criteria for malnutrition	Comments
Hunter, 1981 38 subjects	<90% usual weight	50% weighed <90 % of their usual weight
Openbrier, 1983 77 subjects with emphysema	<90% IBW	43% were malnourished
Gray-Donald, 1989 135 subjects	<90% IBW	24% were malnourished
Wilson, 1989 779 subjects	<90% IBW	24% were malnourished
Schols, 1989 153 subjects	NI comprising 4 parameters Alb, Palb, TLC, %IBW	19% were malnourished according to NI
Sahebjami, 1993 126 subjects	BMI <20 underweight and TSF <10th percentile MAC <5th percentile	23% were underweight
Schols, 1993 253 subjects	<90% IBW and <63% FFMPIBW	26% had reduced body weight and depleted fat-free mass
Laaban, 1993 50 subjects	NI based on anthropometric + biochemical variables	60% were malnourished according to NI includes 39% with >90% IBW

TSF=triceps skinfold, MAC=midarm circumference, IBW=ideal body weight, NI=nutritional index, FFMPIBW=fat-free mass expressed as a percentage of ideal body weight.
Alb=albumin, Palb=prealbumin, TLC=total lymphocyte count

Table 2. Summary of energy expenditure in patients with COPD.

Author	Subjects			Results (mean ± SD) REE/H.B.%pred* (Oxygen cost of ventilation, ml O_2/L)		
Goldstein et al, 1987	10 COPD wt-losing FEV_1 <60%	5 Control malnourished w/o COPD		COPD 116±3	Control 90±1	
Fitting et al, 1989	10 COPD 90% IBW FEV_1 <60%	10 Control 97% IBW		COPD 117±15	Control 95±6	
Donahoe et al, 1989	9 COPD <90% IBW FEV_1 <60%	9 COPD >90% IBW	Control 105% IBW	COPD 119±12 (4.3±1)	COPD 105±20 (2.6±1)	Control 94±6
Wilson et al, 1990	7 COPD 78% IBW FEV_1 <60%	8 COPD 114% IBW	7 Control 105% IBW	COPD 115±2	COPD 99±3	Control 93±2
Schols et al, 1991b	34 COPD wt-losing FEV_1 <60%	34 COPD wt-stable	34 Control	COPD 118±17	COPD 110±11	Control 104±6
Ryan et al, 1993	10 COPD < 85% IBW			COPD 94±16		
Sridhar et al, 1994	6 COPD 77% IBW FEV_1 <60%	6 Scoliosis 95% IBW	6 Control 106% IBW	COPD 104±8	Scoliosis 105±11	Control 103±7

*Percent predicted was determined from sex specific equations of Harris and Benedict.

Table 3. Summary of refeeding trials carried out in stable, malnourished COPD subjects.

Author(s) Duration	N	Baseline kcal	Add kcal	Total Intake	Comments
Wilson et al, 1986 2 weeks	6	2,180 to 3,400 1.1 to 1.76 x BMR mean = 1.4 x BMR	N/A	N=3 > 1.5 x BMR N=3 = 1.5 x BMR	gain of 3 kg, improv in PI_{max}, no change in pulmonary function
Efthimiou et al, 1988 3 months	21	~ 1,429 ~ 53 g protein ~ 1.3 x REE	~ 690 ~ 29 g prot	~ 2,118 kcal ~ 82 g protein ~ 1.9 x REE	wt gain of 4 kg, improv in respir muscle and grip, no changes in lung function
Whittaker et al, 1990 16 days	10	~ 1,489	1,000	~ 2,489 kcal 2.2 x REE	wt gain of 2,4 kg, improv in PE_{max}, no change in FEV_1, FVC
Rogers et al, 1992 3 weeks	27	1.4 x REE	N/A	1.7 x REE 1.5 g prot/kg	wt gain of 1.7 kg, improv in grip and PE_{max}
Knowles et al, 1988 8 weeks	25	~ 1,928 1.5 x REE	~ 422	~ 2,350 kcal ~ 1.8 x REE	no effects on respir muscles or lung function
Lewis et al, 1987 8 weeks	21	~ 1,816 1.5 x H.B.	~ 275	~ 2,091 kcal 1.7 x H.B.	no weight gain, no change in respir muscle or lung function
Sridhar et al, 1994 4 months	12	~ 1,245 1.1 x REE	~ 425	~ 1,670 kcal	no change in weight, FEV_1 or respir muscle
Otte et al, 1989 13 weeks	28	~ 2,319 2 x REE	~ 400	~ 2,719 kcal 2.4 x REE	wt gain of 1.5 kg, no change in PI_{max}, PE_{max}

BMR=basal metabolic rate, REE=resting energy expenditure, H.B=Harris and Benedict equation

Table 4. Baseline characteristics of study population. (mean ± SEM)

Characteristic	N	Control Group	N	Treatment Group	p value
Age (years)	11	68.27±2.60	12	69.83±2.78	0.687
Sex (male:female)	11	7:4	12	8:4	0.885
Weight (kg)	11	63.12±4.39	12	65.11±3.52	0.724
Height (cm)	11	161.00±2.75	12	162.08±3.52	0.813
BMI(kg/m^2)	11	24.20±1.33	12	24.92±1.39	0.716
TSF (mm)	10	8.35±1.07	12	8.92±1.30	0.745
MAC (mm)	10	266.12±12.55	12	267.89±9.53	0.910
Handgrip (kg)	11	26.15±2.12	12	30.36±3.29	0.304
FEV_1 (% pred)	11	29.82±3.72	12	31.33±3.92	0.783
FVC (% pred)	11	69.55±5.36	12	61.67±5.57	0.321
PI_{max} (-cm H_20)	11	68.37±6.00	12	73.25±12.02	0.727
PE_{max} (cm H_20)	11	117.82±5.43	12	113.00±9.26	0.665
Days in hospital (range)	11	3 - 31	12	4 - 33	0.278
6 minute walk (m)	6	170±39	9	261±43	0.164
Dyspnea score (mm)	10	35.45±6.59	12	36.71±1.55	0.841
Total general well-being score (points)	8	55.53±7.87	11	65.40±5.76	0.313
Subscores: (points)					
Anxiety score	8	14.57±2.08	11	19.22±1.63	0.092
Depression score	8	13.44±1.37	11	14.95±1.68	0.519
General health score	8	8.63±1.15	11	9.02±0.66	0.765

Table 5. Biochemical indices of study population. (mean ± SEM)

Variable	N	Control Group	N	Treatment Group	p-value
Albumin g/L	7	38.72±1.39	11	36.56±1.26	0.282
Haematocrit l	8	0.43±0.01	11	0.42±0.01	0.664
Haemoglobin g/L	9	138.66±4.27	11	137.00±4.24	0.787
Leucocyte count $*10^9$/L	8	10.12±0.95	11	12.13±1.26	0.252
glucose mmol/L	10	11.20±1.20	12	9.63±1.09	0.347
methylprednisolone mg/d	11	76.23±9.77	12	63.58±13.26	0.457

Table 6. Baseline characteristics of completed and incompleted subjects. (mean ± SEM)

Characteristic	N	Completed Subjects	N	Incompleted subjects	p-value
Age (years)	16	68.62±2.12	7	70.14±4.03	0.718
Sex (male:female)	16	12:4	7	3:4	0.149
Weight (kg)	16	68.35±3.19	7	54.58±3.14	0.016
Height (cm)	16	164.06±2.56	7	155.85±3.66	0.087
BMI [wt(kg)/ht(m^2)]	16	25.51±1.25	7	22.41±0.87	0.135
TSF (mm)	16	8.31±0.92	6	9.58±1.98	0.515
MAC (mm)	16	272.64±9.71	6	252.27±7.49	0.236
Handgrip (kg)	16	31.14±2.41	7	21.95±2.24	0.030
FEV_1 (% pred)	16	31.31±3.18	7	29.00±5.11	0.698
FVC (% pred)	16	64.18±4.25	7	68.28±8.68	0.637
PI_{max} (-cm H_20)	16	78.31±8.58	7	54.00±7.89	0.099
PE_{max} (cm H_20)	16	118.68±5.92	7	107.57±11.61	0.354
Days in hospital (range)	16	5 - 33	7	3 - 93	0.4689
Methylprednisolone (mg/d)	16	74.57±11.11	7	67.30±16.89	0.7224
Dyspnea score (mm)	14	35.57±4.13	8	37.12±4.44	
Total general well-being score (points)	13	65.81±4.26	6	51.33±11.34	0.157
Anxiety score	13	18.70±1.59	6	14.13±2.25	0.120
Depression score	13	16.18±0.86	6	10.25±2.33	0.008
General health score	13	8.85±0.55	6	8.86±1.58	0.992

Table 7. Energy and macronutrient intake of completed and incompleted subjects.

Variable	N	Complete subjects	N	Incomplete subjects	p-value
Kcal/day	16	2,304±115	5	1,433±124	0.0009
Carbohydrates g/day	16	287±14	5	193±19	0.0036
Protein g/day	16	91±5	5	54±3	0.0007
Fat g/day	16	92±5	5	52±4	0.0009

Values are mean ± SEM

Table 8. Baseline characteristics and changes for completed subjects. (mean ± SEM)

Characteristics	Control Group		Treatment Group			p-value for change
	N	Baseline[1)]	Change	N	Baseline	Change	
Age (years)	6	69.5±3.27	N/A	10	68.1±2.90	N/A	0.761
Weight (kg)	6	70.15±5.96	-0.01±0.22	10	67.27±3.86	+0.23±0.75	0.815
Body mass index [kg/ht(m^2)]	6	26.26±2.04	-0.05±0.08	10	25.07±1.64	0.00±0.28	0.901
FEV_1 % predicted	6	34.83±5.33	-0.16±0.79	10	29.20±4.03	+5.30±2.91	0.178
FVC % predicted	6	73.66±5.04	-4.50±2.14	10	58.50±5.50	+11.10±4.63	0.026
PI_{max} (-cm H_2O)	6	73.00±9.10	+8.00±12.64	10	81.50±12.87	-2.10±3.74	0.363
PE_{max} (cm H_2O)	6	124.50±7.47	-3.00±5.61	10	115.20±8.44	+2.90±4.23	0.412
Grip strength (kg)	6	28.58±3.50	-0.33±0.88	10	32.68±3.28	-1.06±1.27	0.712
Dyspnea score (mm)	6	35.66±9.73	+8.00±6.75	8	36.45±1.86	+14.56±7.73	0.551
6 minute walk (m)	6	171±39	N/A	9	262±43	N/A	0.164
Days in hospital	6	5 - 17	N/A	10	9 - 33	N/A	
Total general well-being (pts)	3	48.00±7.00	+10.00±1.52	8	69.48±5.80	+8.90±5.86	0.914
Subgroups Anxiety (points)	3	10.66±2.66	+3.33±1.20	8	20.40±1.75	+0.67±2.08	0.477
Depression (points)	3	13.33±1.66	+1.33±0.66	8	16.43±1.42	+1.02±0.85	0.840
General health (points)	3	7.33±0.88	+1.66±0.88	8	8.55±0.72	+2.75±0.88	0.506

[1)] Baseline characteristics were similar between the study groups.

Table 9. Energy and Macronutrient intake of completed subjects. (mean ± SEM)

Variable	N	Control Group	N	Treatment Group	p-value
Intake/H.B.[1)]	6	1.43±0.12	10	1.88±0.08	0.008
Kcal/day	6	1,951±130	10	2,516±129	0.012
Kcal/kg·day	6	29±4	10	38±3	0.062
Carbohydrate g/day	6	246±17	10	312±16	0.021
Protein g/day	6	80±6	10	99±6	0.059
Protein/kg·day	6	1.2±0.15	10	1.5±0.11	0.120
Fat g/day	6	77±6	10	102±6	0.020

[1)] ratio of actual intake to estimated intake for basal metabolic needs using the Harris and Benedict equation.

Table 10. Biochemical indices of completed subjects. (mean ± SEM)

Variable	N	Control Group	N	Treatment Group	p-value
Albumin g/L	3	39.00 ± 3.67	9	36.67 ± 1.40	0.477
Haematocrit l	3	0.45 ± 0.04	9	0.42 ± 0.02	0.362
Haemoglobin g/L	4	143.25 ± 8.53	9	137.11 ± 5.05	0.528
Leucocyte count $*10^9$/L	4	10.44 ± 0.57	9	12.18 ± 1.52	0.475
glucose mmol/L	5	8.83 ± 1.19	10	9.66 ± 1.31	0.692
methylprednisolone mg/d	6	70.97 ± 8.43	10	69.95 ± 15.15	0.961

Table 11. Nitrogen balance data.

Variable	N	mean ± SEM
Protein g/kg-day	9	1.28 ± 0.13
Nitrogen balance g N/day	9	-8.42 ± 1.74

Table 12. Relationship between changes in body weight and functional parameters.

Change in weight (kg) and	Pearson Correlation coefficient (r)	p-value	no. of obs.
Change in FEV_1 (%pred)	0.468	0.067	16
Change in FVC (%pred)	0.520	0.039	16
Change in PI_{max} (-cm H_2O)	0.091	0.735	16
Change in PE_{max} (cm H_2O)	0.159	0.555	16
Change in grip strength (kg)	0.726	0.002	15
Change in dyspnea score (mm)	-0.312	0.276	14
Walking distance (m)	0.055	0.844	15

Table 13. Relationship between changes in general well-being and functional parameters.

Changes in general well-being and	Pearson Correlation coefficient (r)	p-value	no. of obs.
Change in FEV_1 (% pred)	-0.205	0.543	11
Change in FVC (% pred)	0.036	0.914	11
Change in PI_{max} (-cm H_2O)	0.021	0.950	11
Change in PE_{max} (cm H_2O)	-0.242	0.473	11
Change in dyspnea score (mm)	0.728	0.026	9
Distance walked (m)	0.454	0.186	10
Days in hospital	-0.481	0.134	11

Table 14. Relationship between nitrogen balance and outcome measures.

Nitrogen balance and	Pearson Correlation coefficient	p-value	N
Change in weight (kg)	0.142	0.715	9
Change in PI_{max} (-cm H_2O)	0.306	0.422	9
Change in PE_{max} (cm H_2O)	0.005	0.990	9
Change in grip strength (kg)	0.504	0.202	8

Table 15. Relationship between methylprednisolone intake and functional status.

Methylprednisolone intake (mg/d) and	Pearson correlation coefficient (r)	p-value	no. of obs.
Change in grip strength (kg)	-0.755	0.001	15
Change in FEV_1 (% pred)	-0.328	0.214	16
Change in FVC (% pred)	-0.453	0.077	16
Change in PI_{max} (-cm H_2O)	0.062	0.818	16
Change in PE_{max} (cm H_2O)	-0.136	0.614	16
Change in well-being	-0.654	0.029	11
Nitrogen balance	-0.731	0.025	9
Change in weight (kg)	-0.330	0.211	16

Table 16. Power and sample size calculations.

Variable	Observed difference	Observed SD[1]	Calculated Power (1-ß)	Expected difference[2]	Power (1-ß)	Required sample size[3]
FEV_1 %predicted	5.46	7.47	0.56	10	0.80	18
FVC %predicted	15.60	12.16	0.95	10	0.80	48
PI_{max} (-cm H_2O)	10.10	20.81	0.28	10	0.80	136
PE_{max} (cm H_2O)	5.90	13.53	0.23	10	0.80	58
Grip strength (kg)	0.73	3.43	0.09	4	0.80	24
Dyspnea score (mm)	6.56	19.83	0.14	10	0.80	124
6 min walk (m)	91	116.95	0.56	90	0.80	54

[1] Pooled estimated standard deviation.
[2] A clinically meaningful difference.
[3] Required sample size taking into account the variability among the study population.

V

APPENDICES

Patient consent form
General well-being questionnaire
Dyspnea score diagram

Patients with emphysema and chronic bronchitis often lose weight as a result of their illness which is associated with losses in strength and diminished resistance to infection. We wish to determine the best way of preventing weight loss in COPD patients while in hospital for an exacerbation.

The study for which you are being asked to participate involves a number of tests soon after entry to hospital and again just prior to discharge. If you are in hospital less than 12 days, you will be asked to come back and repeat these tests. You will be weighed and measured, you will be asked to do some routine lung function tests, and your handgrip strength will be measured by squeezing a small portable apparatus, also we will ask you to collect urine for a 24 hour period. We will also ask you to answer a questionnaire about your health. During your hospital stay, you will receive the standard hospital diet, in addition you may be given supplements to increase your total caloric intake. You will be asked to take these supplements for 2 weeks, whether you are in the hospital or at home. During hospitalization a dietician will visit you each day to find out how you are eating.

Should you wish to discontinue your participation at any time, you are completely free to do so without any consequences to your care.

This research is completely voluntary, and might not lead to improvements in your health, but will help us find a way of providing good nutritional care to COPD patients.

I,_____, have read the above and agree to the tests and procedures outlined above, I understand that I am free to withdraw from the study at any time.

_____ _____

Signature of patient Date

_____

Witness

Les patients qui se présentent avec l'emphysème ainsi que la bronchite chronique souffrent très souvent de pertes de poids attribuables à leur maladie qui s'associe aux diminutions de force et de résistance aux infections.

Nous voulons maintenant déterminer la meilleure façon de prévenir la perte de poids pour des patients hospitalisés résultant d'une aggravation de leur condition. L'étude, dans laquelle nous demandons votre participation, comprend un certain nombre d'examens, effectués à votre arrivée à l'hôpital et répétés avant votre départ. Si vous restez moins de 12 jours à l'hôpital, on vous demandera de revenir pour compléter ces examens. On vous pesera, on vous mesurera et on vous demandera de faire des tests pulmonaires de routine. Au moyen d'un petit appareil portatif, on mesurera votre force musculaire, et on vous demandera de prendre votre urine pour une période de 24 heures. On vous demandera aussi de répondre à un questionnaire au sujet de votre santé générale. Pendant votre séjour à l'hôpital, vous mangerez la nourriture habituelle. En plus, afin d'augmenter votre prise calorique totale, on vous donnera peut-être des suppléments. S'il en est ainsi, on vous demandera de prendre ces suppléments pendant une quinzaine de jours, soit à l'hôpital soit chez vous. Pendant votre séjour à l'hôpital une diététiste vous visitera chaque jour pour voir ce que vous mangez.

Dans le cas ou vous déciderez de discontinuer ce régime, vous êtes libre de le faire sans aucune conséquence à vos soins. Ces recherches sont complètement volontaires et il est possible qu'elles ne produisent pas une amélioration à votre santé. Néanmoins, elles nous aideront à découvrir le meilleur façon d'obtenir la bonne nutrition pour cette condition.

Je soussigné(e)_____, ai lu ce document et je consens aux examens et aux méthodes décrits ci-dessus. Je comprends que j'aurai le droit, n'importe quand, de me retirer de cette étude

et j'ai signé_____ date_____

certifié par _____.

THE GENERAL WELL-BEING SCHEDULE

READ - *This section of the examination contains questions about how you feel and how things have been going with you. For each question, mark (X) the answer which best applies to you*

1. How have you been feeling in general? (SINCE THE LAST 2 WEEKS)

   1 [ ] In excellent spirits
   2 [ ] In very good spirits
   3 [ ] In very good spirits mostly
   4 [ ] I have been up and down in spirits a lot
   5 [ ] In low spirits mostly
   6 [ ] In very low spirits

2. Have you been bothered by nervousness or your "nerves"? (SINCE THE LAST 2 WEEKS)

   1 [ ] Extremely so -- to the point where I could not work or take care of things
   2 [ ] Very much so
   3 [ ] Quite a bit
   4 [ ] Some -- enough to bother me
   5 [ ] A little
   6 [ ] Not at all

3. Have you been in firm control of your behavior, thoughts, emotions OR feelings? (SINCE THE LAST 2 WEEKS)

   1 [ ] Yes, definitely so
   2 [ ] Yes, for the most part
   3 [ ] Generally so
   4 [ ] Not too well
   5 [ ] No, and I am somewhat disturbed
   6 [ ] No, and I am very disturbed

4. Have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile? (SINCE THE LAST 2 WEEKS)

   1 [ ] Extremely so -- to the point that I have just about given up
   2 [ ] Very much so
   3 [ ] Quite a bit
   4 [ ] Some -- enough to bother me
   5 [ ] A little bit
   6 [ ] Not at all

5. Have you been under or felt you were under any strain, stress, or pressure? (SINCE THE LAST 2 WEEKS)

   1 [ ] Yes -- almost more than I could bear or stand
   2 [ ] Yes -- quite a bit of pressure
   3 [ ] Yes -- some - more than usual
   4 [ ] Yes -- some - but about usual
   5 [ ] Yes -- a little
   6 [ ] Not at all

6. How happy, satisfied, or pleased have you been with your personal life? (SINCE THE LAST 2 WEEKS)

   1 [ ] Extremely happy -- could not have been more satisfied or pleased
   2 [ ] Very happy
   3 [ ] Fairly happy
   4 [ ] Satisfied -- pleased
   5 [ ] Somewhat dissatisfied

7. Have you had any reason to wonder if you were losing your mind, or losing control over the way you act, talk, think, feel, or of your memory? (SINCE THE LAST 2 WEEKS)

1 [ ] Not at all
2 [ ] Only a little
3 [ ] Some -- but not enough to be concerned or worried about
4 [ ] Some and I have been a little concerned
5 [ ] Some and I am quite concerned
6 [ ] Yes, very much so and I am very concerned

8. Have you been anxious, worried, or upset? SINCE THE LAST 2 WEEKS)

1 [ ] Extremely so -- to the point of being sick or almost sick
2 [ ] Very much so
3 [ ] Quite a bit
4 [ ] Some -- enough to bother me
5 [ ] A little bit
6 [ ] Not at all

9. Have you been waking up fresh and rested? (SINCE THE LAST 2 WEEKS)

1 [ ] Every day
2 [ ] Most every day
3 [ ] Fairly often
4 [ ] Less than half the time
5 [ ] Rarely
6 [ ] None of the time

10. Have you been bothered by any illness, bodily disorder, pains, or fears about your health? (SINCE THE LAST 2 WEEKS)

1 [ ] All of the time
2 [ ] Most of the time
3 [ ] A good bit of the time
4 [ ] Some of the time
5 [ ] A little bit of the time
6 [ ] None of the time

11. Has your daily life been full of things that were interesting to you? (SINCE THE LAST 2 WEEKS)

1 [ ] All the time
2 [ ] Most of the time
3 [ ] A good bit of the time
4 [ ] Some of the time
5 [ ] A little of the time
6 [ ] None of the time

12. Have you felt down-hearted and blue? (SINCE THE LAST 2 WEEKS)

1 [ ] All the time
2 [ ] Most of the time
3 [ ] A good bit of the time
4 [ ] Some of the time
5 [ ] A little of the time
6 [ ] None of the time

13. Have you been feeling emotionally stable and sure of yourself? (SINCE THE LAST 2 WEEKS)

1 [ ] All the time
2 [ ] Most of the time
3 [ ] A good bit of the time
4 [ ] Some of the time
5 [ ] A little of the time
6 [ ] None of the time

14. Have you felt tired, worn out, used-up, or exhausted? (SINCE THE LAST 2 WEEKS)

1 [ ] All the time
2 [ ] Most of the time
3 [ ] A good bit of the time
4 [ ] Some of the time
5 [ ] A little of the time
6 [ ] None of the time

For each of the four scales below, note that the words at each end of the 0 to 10 scale describe opposite feelings. Circle any number along the bar which seems closest to how you have generally felt SINCE THE LAST SIX WEEKS.

15. How concerned or worried about your HEALTH have you been? (SINCE THE LAST 2 WEEKS)

0 1 2 3 4 5 6 7 8 9 10

not concerned at all — very concerned

16. How RELAXED or TENSE have you been? (SINCE THE LAST 2 WEEKS)

0 1 2 3 4 5 6 7 8 9 10

very relaxed — very tense

17. How much ENERGY, PEP, VITALITY have you felt? (SINCE THE LAST 2 WEEKS)

0 1 2 3 4 5 6 7 8 9 10

no energy AT ALL, listless — very RELAXED, dynamic

18. How DEPRESSED or CHEERFUL have you been? (SINCE THE LAST 2 WEEKS).

0 1 2 3 4 5 6 7 8 9 10

very depressed — very cheerful

Ce test vise à mesurer votre essoufflement. Imaginez que cette ligne est une règle. Le bas de la ligne représente un essoufflement extrême alors que le haut ne représente aucune essoufflement. Des activités quotidiennes sont indiquées au côté de la ligne. En lisant de bas en haut, vous trouverez des activités demandant très peu d'effort physique et à mesure que vous montez, chaque activité demande plus d'effort. Par exemple, se laver demande plus d'effort que rester assis.

J'amerais que vous fassiez une marque sur la ligne à l'endroit qui decrit le mieux votre limitation. (SI UN PATIENT DIT NE FAIRE AUCUNE ACTIVITE EN PARTICULIER, DEMANDEZ LUI D'EVALUER CE QU'IL OU QU'ELLE PENSE POUVOIR FAIRE SI C'ETAIT NECESSAIRE).