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NUTRITION IN CLINICAL CARE (J PATEL, SECTION EDITOR)

Interstitial Lung Disease, Body Mass Index, Energy Expenditure and Malnutrition—a Review

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Abstract
Purpose of Review Interstitial lung disease (ILD) comprises a spectrum of chronic disorders that cause various degrees of inflammation or fibrosis in the pulmonary interstitium. Although limited, data exists on nutritional concerns in ILD. However, previous research has not fully explored the broad range of potential nutritional concerns in ILD and impacts on outcomes. The purpose of this review was to identify and describe the overall nutritional status and relating concerns within the ILD population.
Recent Findings Appropriate weight management in this population may positively impact both pre- and post-transplant survival. Additionally, accounting for adequate muscle mass may predict better outcomes than considering body mass index alone. Current research has identified risk of malnutrition related to decreased muscle strength, increased energy expenditure, vitamin D deficiency, and increased risk of osteoporosis and osteopenia.
Summary Current research is preliminary and further research is necessary to identify established nutritional complications in this population.

Keywords Interstitial lung disease · Body mass index · Energy expenditure · Malnutrition · Nutrition · Critical care

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Introduction

Interstitial lung disease (ILD) comprises a spectrum of chronic disorders that cause various degrees of inflammation or fibrosis in the pulmonary interstitium [1]. A common ILD is idiopathic pulmonary fibrosis (IPF). IPF involves exclusively the lungs, is characterized by progressive fibrosis and architectural distortion of the lung parenchyma and is relentlessly progressive, with a dismal prognosis [2]. While the aetiology of some ILD, including IPF, remains unknown [3], some other are caused by occupational, inorganic or organic exposures, drug-induced toxicities, or are secondary to connective tissue disease [1]. While the clinical course and outcome of ILD other than IPF are highly variable between different subtypes [1], survival after diagnosis of IPF is only 2.5 to 5 years [4, 5].

Medical therapeutic options vary among different types of ILD and include immunosuppressive therapy [6, 7], anti-fibrotic agents [8, 9] and, when medical therapy fails in eligible patients, lung transplantation (LTx) [2]. Regardless of the aetiology, however, the management strategy of ILD also includes supportive therapy including home oxygen [10] and pulmonary physiotherapy [11]. However, little is known about the relationship of nutrition on clinical course, a potentially important implication on the outcome of ILD patients and quality of life of these patients.

Body Mass Index

ILD and IPF, in particular, represent one of the major indications for lung transplantation referrals in Canada and around the world [12, 13]. In Canada, approximately 26% of bilateral lung and approximately 44% of single lung transplants between 2004 and 2013 occurred in patients with a primary diagnosis of IPF [13]. Previous studies have suggested that

nutritional status pre-LTx may improve outcomes post-LTx which opposes the concept that increased BMI offers protective effects [14, 15]. One study, which included IPF patients as a portion of the transplant sample, reported that lung transplant patients with BMIs >27 kg/m^2 had an increased odds ratio of 5.0 (1.4–14.6 95% CI) ($p = 0.003$) of death within 90 days post-LTx [15]. Additionally, a trend was determined toward increased mortality 90 days post-LTx in patients with BMIs <17 kg/m^2 [15]. Other recent studies have also demonstrated increased mortality at 1-year post-transplant in underweight (BMI <18.5 kg/m^2) and obesity (BMI ≥ 30.0 kg/m^2) [16, 17]. These studies have failed to address the influence of composition on mortality. For instance, a recent study by Singer et al. found that when accounting for body composition, a BMI of 30.0–34.9 kg/m^2 was no longer associated with 1-year mortality which conflicts this large body of research that exists to date [18•].

Body mass (both under- and overweight) of patients with ILD impacts their breathing and health status. Patients with greater weight losses (especially lean mass) have the greatest deterioration in lung function, while obesity complicates breathing and results in an increased workload and decreased performance [19]. Thus, in general, improving any patients' nutritional status through appropriate weight management should lead to an improved quality of life. Interestingly, increased body mass index (BMI) has been found to be correlated with an increased survival rate in IPF patients [4, 20]. Alakhras et al. found that BMI values greater than 30 kg/m^2 had a protective effect on morbidity of IPF patients as compared to BMI groups 25–30 and <25 kg/m^2 [20]. Although, it is important to note that the aforementioned study did not adjust for other known predictors of mortality including age, sex, nor lung function. It has been well documented that BMI is a good prognostic sign in other lung diseases such as chronic obstructive pulmonary disease (COPD) [21–26]. However, only a few studies have demonstrated this effect in IPF patients and no studies have demonstrated the protective effects of increased BMI in other non-IPF ILD cases [4, 20]. The concept of obesity being protective suggests an inverse epidemiology, in that, obesity may potentially offer protection against malnutrition, offer better nutritional status, and protect against the effects of medical treatments [20].

As with the transplant population, current research has failed to consider the impact of body composition in the protective effect of increased BMI in ILD patients. A burgeoning area of research involves the investigation of sarcopenia and sarcopenic obesity. Presence of sarcopenia has been found to be associated with increased mortality, infection and hospital length of stay [27]. Currently, no data exists on the influence of muscle mass on outcomes in individuals with ILD; however, Mendes et al. recently identified skeletal muscle atrophy and weakness in individuals with advanced ILD on the waiting list for lung transplant [28]. It has been well established that failing to meet protein requirements in older adulthood may exacerbate chronic illness and other associated health challenges associated such as wound healing, illness recovery and bone health [29]. Thus, an interesting area of research to explore further should focus on relationships between sarcopenia, protein intake and functional outcomes.

Energy Expenditure

The use of indirect calorimetry and bioelectrical impedance analysis (BIA) to determine resting energy expenditure (REE) is well documented in other lung disease states such as COPD [30, 31], but little research has been published on the prevalence of hyper- and hypometabolism in patients with ILD. Previous studies involving COPD patients have demonstrated that REE is highly variable and cannot be accurately predicted via body weight measures or predictive equations such as the Harris Benedict Equation (HBE) [31, 32]. This has great significance as it has been shown that nearly half of COPD patients become underweight in their disease progression [30]. Although aetiology varies between constrictive versus restrictive pulmonary disease, in both, dyspnea is common [30, 33]. It is likely that this laboured breathing could increase the cost of breathing in ILD and result in weight loss and malnutrition in worsening ILD.

Only one study of small sample size, to date, has measured REE. Fitting et al. report a mean REE via indirect calorimetry of 1.16 ± kcal/min in a sample of 12 individuals with ILD [34]. Authors compared this value to three REE prediction equations, the Fleisch equation, the Harris Benedict Equation, and a fat-free mass-based equation as previously determined by the authors. When compared to the Fleisch and Harris-Benedict Equation, measured REE was found to be 117.3 ± 3.2% ($p < 0.001$) and 118.7 ± 3.8% ($p < 0.001$) of predicted REE, respectively [34]. And, when compared to the fat-free mass-based equation, measured REE was found to be 120.8 ± 2.7% ($p < 0.001$) of predicted REE [34]. Better understanding the prevalence of hyper- and hypometabolism has great significance as malnutrition and loss of lean body mass may result in a decreased survival rate [35]; thus, accurate measurement of REE may help to determine appropriate nutritional needs to prevent malnutrition.

Malnutrition

Subjective global assessment (SGA) is a component of nutritional assessment, which ranks severity of malnutrition through subjective measures and is considered the gold-standard of malnutrition assessment [36]. To the best of our knowledge, no previous studies have assessed malnutrition using SGA in the ILD patient population. However, in

other lung diseases such as COPD, studies have identified 40–83% of patients as mildly to severely malnourished [37, 38]. An American study evaluated the nutritional status of IPF patients and aimed to gauge the appropriateness of the Mini Nutrition Assessment®-Short Form (MNA-SF), a malnutrition-risk tool designed for individuals >65 [39]. Results from a poster presentation revealed approximately one quarter of participants were at risk of malnutrition while the remaining were identified as normal nutritional status, however, authors concluded that the application of MNA-SF in the general IPF population was not appropriate due to wide range of ages [39].

Medications, such as, glucocorticosteroids, and protein pump inhibitors (PPIs) or H2 antagonists for management of gastroesophageal reflux disease resulting from the adverse effects of pirfenidone are commonly prescribed in ILD management [40–42]. Additionally, it has been reported that ILD affects middle-aged and older adults, as two thirds of ILD patients are over the age of 60 years [5]. Nutritional deficiencies associated with aging [40, 41], confounded by nutrient-drug interactions common in the ILD population [43] warrants investigation into potential deficiencies. For example, decreased gastric acid due to aging and PPI/H2 antagonist use may limit the absorptive capacity of vitamin B12, and other physiological changes common in aging such as reduced synthesis by the skin, impaired conversion by the kidneys and altered absorption confounded by glucocorticoids can lead to vitamin D deficiency [44, 45]. Researchers must first identify nutritional deficiencies in the ILD population before determining whether aetiologies are related to ILD or to other factors.

Not surprisingly, minimal data exist on micronutrient concerns in ILD. However, some research exists related to vitamin D and calcium. Research has suggested a potential role of vitamin D deficiency and lung disease severity [46–50]. Higher rates of mortality in ILD patients have been reported in winter months when vitamin D status is generally decreased [49]. The evidence on the link between vitamin D and ILD is epidemiologic data and it is unknown if vitamin D deficiency is a direct result of lung disease. Thus, the link between vitamin D and ILD remains hypothetical as the mechanism through which vitamin D offers protective effects in ILD has not yet been determined nor demonstrated. Additionally, a study by Alhamad and Nadama found a high prevalence of osteoporosis and osteopenia, 44 and 35%, respectively, in their sample of $n = 196$, newly diagnosed ILD patients [51••]. Increased risk of osteoporosis was found to be associated with increased age, hypertension, diabetes mellitus, decreased partial pressure of carbon dioxide and usual interstitial pneumonia (UIP). Additionally, those without osteoporosis had significantly greater 6-min walk distances than those without osteoporosis ($p = 0.001$). Interestingly, mean serum 25-hydroxy vitamin D was not significantly different between those with osteoporosis (42.4 ± 30.5 nmol/L) and those with osteoporosis (38.8 ± 26.7 nmol/L) ($p = 0.423$) and indicated deficiency in both groups [51••]. Corticosteroid use can increase the risk of osteoporosis, however, in this study, authors found that corticosteroid use was not significantly different between groups [51••]. It is important to note that a full history of previous use and duration of corticosteroids prior to participants presenting to their clinic could not be obtained; thus, corticosteroid use cannot be removed as a risk factor of osteoporosis based on these results. The results from this study highlight the need for early identification of osteoporosis and its associated risk factors followed by prophylactic treatments in the ILD patient population.

Currently, there are no effective treatments for ILD, aside from lung transplantation. Despite the potential for nutrition interventions to significantly impact clinical outcomes, the investigation of the nutritional status of patients with ILD is notably limited in the literature. However, we must first determine nutritional status of this population or at very least identify nutritional deficiencies that may or may not affect the work of breathing to better serve this population. There is reason to believe that individuals with ILD could benefit from proactive nutrition assessment as some research has identified risk of malnutrition related to decreased muscle strength, increased energy expenditure, vitamin D deficiency, and increased risk of osteoporosis and osteopenia. This review provides novel insight into the nutritional status of ILD patients; however, it is important that research continues to better understand the nutritional concerns of individuals with ILD and to establish targetable nutrition problems in this population.

Compliance with Ethical Standards

Conflict of Interest Marco Mura, Janet Madill, and Sylvia Renaldi declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008;63 Suppl 5:v1–58.
2. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic

pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824.
3. Travis WD, Costabel U, Hansell DM, King TE, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733–48.
4. Mura M, Porretta MA, Bargagli E, Sergiacomi G, Zompatori M, Sverzellati N, et al. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. Eur Respir J. 2012;40(1):101–9.
5. Collard H, King T, Bartelson B, Vourlekis J, Schwarz M. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;168(5):538–42.
6. Richeldi L, Davies HHRHR, Spagnolo P, Luppi F. Corticosteroids for idiopathic pulmonary fibrosis. The Cochrane Collaboration, Richeldi L, editors. Database Syst Rev. 2003;(3):1–13.
7. Spagnolo P, Del Giovane C, Luppi F, Cerri S, Balduzzi S, Walters EH, et al. Non-steroid agents for idiopathic pulmonary fibrosis. The Cochrane Collaboration, editor. Cochrane Database Syst Rev. 2010;(9):1–74.
8. Hunninghake GM. A new hope for idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2142–3.
9. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82.
10. Crockett AJ, Cranston JM, Antic N. Domiciliary oxygen for interstitial lung disease. The Cochrane Collaboration, Crockett A, editors. Cochrane Database Syst Rev. 2001;(3):CD002883.
11. Holland AE, Hill C. Physical training for interstitial lung disease. The Cochrane Collaboration, Holland AE, editors. Cochrane Database Syst Rev. 2008;(4).
12. Yusen RD, Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, et al. The registry of the international society for heart and lung transplantation: thirtieth adult lung and heart-lung transplant report—2013; focus theme: age. J Heart Lung Transplant. 2013;32(10):965–78.
13. CIHI. Canadian organ replacement register annual report: Treatment of end-stage organ failure in Canada, 2004 to 2013 [Internet]. 2014 [cited 2016 Mar 18]. p. 1–129. Available from: https://secure.cihi.ca/free_products/2015_CORR_AnnualReport_ENweb.pdf.
14. Madill J, Maurer JR, de Hoyos A. A comparison of preoperative and postoperative nutritional states of lung transplant recipients. Transplantation. 1993;56(2):347–50.
15. Madill J, Gutierrez C, Grossman J, Allard J, Chan C, Hutcheon M, et al. Nutritional assessment of the lung transplant patient: body mass index as a predictor of 90-day mortality following transplantation. J Heart Lung Transplant. 2001;20(3):288–96.
16. Culver DA, Mazzone PJ, Khandwala F, Blazey HC, Decamp MM, Chapman JT. Discordant utility of ideal body weight and body mass index as predictors of mortality in lung transplant recipients. J Heart Lung Transplant. 2005;24(2):137–44.
17. Gries CJ, Bhadriraju S, Edelman JD, Goss CH, Raghu G, Mulligan MS. Obese patients with idiopathic pulmonary fibrosis have a higher 90-day mortality risk with bilateral lung transplantation. J Heart Lung Transplant. 2015;34(2):241–6.
18.• Singer JP, Peterson ER, Snyder ME, Katz PP, Golden JA, D'Ovidio F, et al. Body composition and mortality after adult lung transplantation in the United States. Am J Respir Crit Care Med. 2014;190(9):1012–21. **This study provides novel insight into the relationship between body composition and outcomes. Previous research mainly focuses on BMI, however, authors have shown that results based on BMI alone do not yield the same results when one accounts for skeletal muscle mass**.
19. Tynan C, Hasse JM. Current nutrition practices in adult lung transplantation. Nutr Clin Pract. 2004;19(6):587–96.
20. Alakhras M, Decker PA, Nadrous HF, Collazo-Clavell M, Ryu JH. Body mass index and mortality in patients with idiopathic pulmonary fibrosis. Chest. 2007;131(5):1448–53.
21. Celli B, Cote C, Marin J, Casanova C, Montes de Oca M, Mendez R, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005–12.
22. Cano N, Raphael J-C, Roth CM, Pichard C, Roth H, Isabelle C, et al. C-reactive protein and body mass index predict outcome in end-stage respiratory failure. Chest. 2004;126(2):540–6.
23. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;160(6):1856–61.
24. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157(6 Pt 1):1791–7.
25. Chailleux E, Fauriux B, Binet F. Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation: a 10-year analysis of ANTADIR Observatory. Chest. 1996;109(2):741–9.
26. Wilson DO, Rogers RM, Wright EC, Anthonisen NR. Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. Am Rev Respir Dis. 1989;139(6):1435–8.
27. Gonzalez M, Pastore CA, Orlandi SP, Heymsfield SB. Obesity paradox in cancer: new insights provided by body composition. Am J Clin Nutr. 2014;99(5):999–1005.
28.• Mendes PO, Wickerson L, Helm DE, Janaudis-ferreira TA, Brooks D, Singer LIG, et al. Skeletal muscle atrophy in advanced interstitial lung disease. 2015;20(6):953–9. **This study focuses on physical activity in ILD and provides novel data on physical functionality. Implications from this research is directly related to nutrition as exercise training and rehabiliation may be enhanced by adequate nutrition intake**.
29. Cawood AL, Elia M, Stratton R. Systematic review and meta-analysis of the effects of high protein oral nutritional supplements. Ageing Res Rev. 2012;11(2):278–96.
30. Slinde F, Grönberg AM, Svantesson U, Hulthén L, Larsson S. Energy expenditure in chronic obstructive pulmonary disease-evaluation of simple measures. Eur J Clin Nutr. 2011;65(12):1309–13.
31. Nordenson A, Gronberg AM, Hulthen L, Larsson S, Slinde F. A validated disease specific prediction equation for resting metabolic rate in underweight patients with COPD. Int J Chron Obstruct Pulmon Dis. 2010;5:271–6.
32. Slinde F, Grönberg A, Svantesson U, Hulthén L, Larsson S. Energy expenditure in chronic obstructive pulmonary disease—evaluation of simple measures. Eur J Clin Nutr. 2011;65(12):1309–13.
33. Ryerson CJ, Collard HR, Pantilat SZ. Management of dyspnea in interstitial lung disease. Curr Opin Support Palliat Care. 2010;4(2):69–75.
34. Fitting J, Frascarolo P, Jequier E, Leuenberger P. Energy expenditure in interstitial lung disease. Am Rev Respir Dis. 1990;142(3):631–5.
35. Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. Clin Nutr. 2008;27(1):5–15.
36. Detsky A, McLaughlin JR, Baker J. What is subjective global assessment of nutritional status? JPEN. 1987;11(1):8–13.
37. Günay E, Kaymaz D, Selçuk NT, Ergün P, Sengül F, Demir N. Effect of nutritional status in individuals with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation. Respirology. 2013;18:1217–22.

38. Gupta B, Kant S, Mishra R. Subjective global assessment of nutritional status of chronic obstructive pulmonary disease patients on admission. Int J Tuberc Lung Dis. 2010;14(4):500–5.
39. Autore K, Black T, Klesen M, Richards T, Gibson K, Kaminski N, et al. Evaluating nutritional status of patients with idiopathic pulmonary fibrosis: a prospective pilot study using the mini nutrition assessment short from. In: A42 Interstitial Lung Disease: Epidemiology, Evaluation and Pathogenesis. Philadelphia Pennsylvania: American Thoracic Society; 2013. p. A1461–A1461.
40. Buhr G, Bales CW. Nutritional supplements for older adults: review and recommendations–Part II. J Nutr Elder. 2010;29(1):42–71.
41. Buhr G, Bales CW. Nutritional supplements for older adults: review and recommendations—part I. J Nutr Elder. 2009;28(1):5–29.
42. McCaddon A. Vitamin B12 in neurology and ageing; clinical and genetic aspects. Biochimie. 2013;95(5):1066–76.
43. Arai T, Inoue Y, Sasaki Y, Tachibana K, Nakao K, Sugimoto C, et al. Predictors of the clinical effects of pirfenidone on idiopathic pulmonary fibrosis. Respir Investig. 2014;52:136–43.
44. de Groot L. Nutritional issues for older adults: addressing degenerative ageing with long-term studies. Proc Nutr Soc. 2016;75(2):169–73.
45. Lems WF, Van Veen GJ, Gerrits MI, Jacobs JW, Houben HH, Van Rijn HJ, et al. Effect of low-dose prednisone (with calcium and calcitriol supplementation) on calcium and bone metabolism in healthy volunteers. Br J Rheumatol. 1998;37(1):27–33.
46. Finklea JD, Grossmann RE, Tangpricha V. Vitamin D and chronic lung disease: a review of molecular mechanisms and clinical studies. Adv Nutr. 2011;2(3):244–53.
47. Hagaman J, Panos R, McCormack F, Thakar C, Wikenheiser-Brokamp K, Shipley R, et al. Vitamin D deficiency and reduced lung function in connective tissue-associated interstitial lung diseases. 2011;139(2):353–60.
48. Mascitelli L, Pezzetta F, Goldstein MR, Waschki B, Kirsten A. Vitamin D and mortality from pulmonary fibrosis a positive end-expiratory pressure effect. Chest. 2010;137(2):495–6.
49. Olson A, Swigris J, Raghu G, Brown KK. Seasonal variation: mortality from pulmonary fibrosis is greatest in the winter. Chest. 2009;136(1):16–22.
50. Ramirez A, Wongtrakool C, Welch T, Steinmeyer A, Zugel U, Roman J. Vitamin D inhibition of pro-fibrotic effects of transforming growth factor beta1 in lung fibroblasts and epithelial cells. J Steroid Biochem Mol Biol. 2010;118(3):142–50.
51.•• Alhamad EH, Nadama R. Bone mineral density in patients with interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis. 2015;32:151–9. **This study identified osteoporosis and ostepenia and a clinically signicant portion of their sample. Authors found that increasing age, UIP diagnosis, higher partial pressure of carbon dioxide, hypertension and diabetes**.