Make No Bones About It
Increasing Epidemiologic Evidence Links Vitamin D to Pulmonary Function and COPD

Highlighting the article by Black and colleagues1 in the current issue of CHEST (see page 3792) on the association between vitamin D and lung function is important for many reasons. Reduced maximally attained lung function and the accelerated decline of pulmonary function are markers of an individual’s increased susceptibility to COPD, which is a potentially preventable disease with significant health and economic impact in the United States and worldwide.2,3 Moreover, reduced lung function is a major risk factor for cardiovascular morbidity and mortality, independent of smoking.4 Thus, while historically dubbed the “Cinderella pulmonary condition,” we are seeing a well-deserved increase in research support, studies, and publications related to COPD and determinants of lung function given the projected growing public health impact.2,5 The factors examined thus far in epidemiologic studies, including smoking, which has received the most attention, account for only a portion of the risk,6 suggesting that adult lung function is influenced by as-yet-undefined chemical, psychological, behavioral, or biological factors that influence host susceptibility.

Black and colleagues1 examined the relationship between serum vitamin D levels and lung function in a cross-sectional analysis of the Third National Health, Nutrition and Examination Survey, a large representative sample (approximately 14,000 subjects) of the US population. They examined the relationship between percent predicted FEV1 and FVC values and the circulating concentration of 25-hydroxyvitamin D, and demonstrated a significant relationship between higher vitamin D levels and increased lung function with a suggested dose-response effect.

Epidemiologic observational studies suggest associations but do not prove causality. Rather, the inference that the observed association represents a cause-effect relationship should be considered in light of a number of epidemiologic criteria for causality, as follows: biological plausibility; strength of the association; reduced likelihood of alternative explanations due to confounding; temporal sequence of events; dose-response relationship; and consistency across studies in different populations.

EVIDENCE SUPPORTING BIOLOGICAL PLAUSIBILITY

Evidence is increasing that suggests an expanded role for vitamin D in health outcomes apart from its classic actions on the gut and bone. The vitamin D3 metabolite, 1,25-dihydroxyvitamin D3 and its synthetic analogs also have potent antiproliferative, differentiative, and immunomodulatory activities, exerting these effects through the vitamin D receptor (VDR). The authors cite evidence linking vitamin D to modulation of the formation of metalloproteinases and fibroblast proliferation, which is involved in lung remodeling, as potential pathways through which vitamin D may influence lung function. Other evidence has demonstrated the expression of the VDR in various immune cells with documented effects of vitamin D on many immune cell types involved in both innate and adaptive immunity.7 At the same time, evolving research has demonstrated interrelationships between immune-mediated inflammatory processes and chronic lung disease. Airway inflammation is recognized as a central process in the pathogenesis of COPD.9 Vitamin D has been shown to prevent the induction of experimental inflammatory diseases in mice including allergic asthma.9 In turn, atopy and various asthma-like phenotypes have been linked to reduced lung function10 and increased morbidity and mortality related to COPD.11 Hypovitaminosis D has also been linked in animal studies to enhanced oxidative stress,12 which is another purported mechanism underlying COPD risk.13 Genetic susceptibility studies14 have linked variants in the VDR to an increased risk of COPD. Studies15,16 examining the association between VDR variants and the rate of decline in pulmonary function among smokers have had mixed results. These overlapping data suggest a role for vitamin D in
chronic inflammatory responses in the lung, which in turn contribute to lung function over time.

NEED FOR FURTHER EPIDEMIOLOGIC EVIDENCE

Consistency across studies provides a compelling basis for causal inferences in epidemiologic research. Examining the same hypothesized relationship between levels of vitamin D and pulmonary function in diverse populations will be important. Seeing a similar relationship across different studies involving different sample populations controlling for potential confounders in various ways, strengthens the case for causality. Observing a dose-response relationship, as suggested in the current study by Black and colleagues,1 provides further suggestive evidence of causality. This cross-sectional analysis cannot discern temporal associations. Longitudinal data supporting the role for vitamin D in the rate of decline of lung function will be important. Before researchers embark on randomized controlled trials, as the authors suggest, they would be helped by taking advantage of other large existing data sets in which the association between vitamin D and lung function can be further examined. It will likely be necessary to design future observational studies that specifically address the influence of vitamin D and lung function in which careful attention is paid to measuring the potential confounders. Often, when secondary data analysis is performed to examine a hypothesis other than the aims intended in the original study, key confounders are measured either inadequately or not at all with consequential effects on any inferences being made.17

It will also be important to consider interactions among a number of these environmental and host factors contributing to lung function rather than simply controlling for them as potential confounders.18 For example, in addition to vitamin D other environmental exposures are known to operate through oxidative stress pathways (eg, tobacco smoke and air pollutants). It has also been suggested19 that hypovitaminosis D increases the susceptibility to psychological stress. There is evidence that psychological stress augments oxidative stress and modifies the host response to other inflammatory oxidative toxins such as tobacco smoke and air pollutants. Thus, cumulative factors that may modify oxidative toxicity may have additive or multiplicative effects on lung function. Vitamin D may interact with stress, tobacco smoke, and air pollutants through an oxidative/antioxidative imbalance, influencing lung inflammation and consequently lung function.20 Future studies should also consider gene-environment interactions that may further elucidate the underlying mechanisms.

SHEDDING LIGHT ON SOCIODEMOGRAPHIC FACTORS AND LUNG FUNCTION

Nutritional habits, levels of nutrients, and dietary factors such as vitamin D intake can vary based on sociodemographic factors including gender, age, and socioeconomic status.21 Similarly, physical activity levels may differ across certain subgroups.22 It will be important for future studies to examine how the relationship between vitamin D and these other factors might explain differential effects on lung function and COPD risk in susceptible subgroups (eg, based on socioeconomic status, gender, and race/ethnicity).23,24

FURTHER EVIDENCE OF THE PUBLIC HEALTH IMPORTANCE

Finally, in addition to the disturbing projected trends for COPD, epidemiologic studies have suggested that hypovitaminosis D is reemerging as an important public health problem in the United States and worldwide.25 It will be important to conduct other studies examining the relationship between vitamin D and lung function, as this would be a relatively simple low-cost intervention that would likely have high compliance to potentially prevent or slow the loss of lung function in susceptible subgroups. More data are needed to suggest which groups might be helped most by such interventions.

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Rehabilitation and the National Emphysema Treatment Trial

A lthough pulmonary rehabilitation is accepted by many professional societies as the prevailing standard of care for patients with chronic lung disease, large observational studies that examine key outcomes such as survival, functional exercise capacity, or health-related quality of life have been slow in coming. Trials of lung volume reduction surgery, the largest of which has been the National Emphysema Treatment Trial (NETT), although not originally designed for this purpose, have enabled us to observe the influence of rehabilitation on a large population of patients with COPD. The NETT design required patients to agree to undergo 6 to 10 weeks of rehabilitation prior to randomization as a prerequisite to enrollment. This requirement was probably a consequence of the positive experiences among the surgical community when their patients received pulmonary rehabilitation in association with major thoracic surgery, as well as the key roles in the NETT played by many of the pulmonary rehabilitation leaders in the United States.

The article by Ries and colleagues in this issue of CHEST (see page 3799) describes the results of a prospective observational study of 1,218 patients who underwent pulmonary rehabilitation in both academic (17 NETT) and community (539 satellite) centers. The numbers alone make this an unusual report, as trials of respiratory rehabilitation are usually single-center randomized controlled trials with relative small numbers, such that even metaanalyses do not come close to the number of patients included in this report.

The authors evaluated the influence of rehabilitation in a national cross-section of programs, an important observation regarding the application of this approach in the real world. Without doubt there is a need for such pragmatic observations. Nevertheless, clinicians reading this report should be mindful of the design limitations of any observational study as well as the specific limitations of this study.

The program content included 16 to 20 sessions with the essential ingredient of exercise training, for which we have excellent evidence of effectiveness, as well the other two main ingredients of education and psychological support, for which the evidence of effectiveness is less clear. Although the initial four sessions were at the local NETT center, subsequent sessions were often outsourced, under supervision, to the local satellites.

The initial patient profile reflected the patients having severe airflow limitation, a marked exercise impairment, and a reduction in health-related qual-