Metabolic Disorders in Chronic Lung Diseases

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Chronic lung diseases represent complex diseases with gradually increasing incidence, characterized by significant medical and financial burden for both patients and relatives. Their increasing incidence and complexity render a comprehensive, multidisciplinary, and personalized approach critically important. This approach includes the assessment of comorbid conditions including metabolic dysfunctions. Several lines of evidence show that metabolic comorbidities, including diabetes mellitus, dyslipidemia, osteoporosis, vitamin D deficiency, and thyroid dysfunction have a significant impact on symptoms, quality of life, management, economic burden, and disease mortality. Most recently, novel pathogenetic pathways and potential therapeutic targets have been identified through large-scale studies of metabolites, called metabolomics. This review article aims to summarize the current state of knowledge on the prevalence of metabolic comorbidities in chronic lung diseases, highlight their impact on disease clinical course, delineate mechanistic links, and report future perspectives on the role of metabolites as disease modifiers and therapeutic targets.

Keywords: chronic lung diseases, metabolic disorders, comorbidities, metabolomics, pathogenetic pathways

INTRODUCTION

Chronic lung diseases, including chronic obstructive pulmonary disease (COPD), asthma, and interstitial lung diseases (ILDs) constitute complex diseases with gradually increasing incidence, mortality, and major medical and financial burden (1). To this end, their management requires a comprehensive multidisciplinary and personalized approach, involving assessment of comorbid conditions (2). Most recently, evidence supports the role of endocrine system dysfunction in the pathogenesis of chronic lung diseases, and thus clinicians have integrated metabolic disorders in the Venn diagram of comorbidities of chronic lung diseases (3) (Figure 1). In particular, metabolic comorbidities exert a major impact on patients’ quality of life and mortality (1, 4). Diabetes mellitus, dyslipidemia, osteoporosis, and thyroid diseases (hypothyroidism and hyperthyroidism) are among the most commonly reported metabolic comorbidities in patients with chronic lung disease (5–8). Genes, age, and nutrition represent the three pillars of cellular metabolism and have been the topic of increasing scientific research in respiratory diseases (9, 10). This review article intends to summarize the most frequent metabolic comorbidities in association with their impact on chronic lung
diseases, as well as to report future perspectives for their role in disease management.

**METABOLIC DISORDERS AND COPD**

There is a compelling interest that COPD is a lung disease not only restricted to airway inflammation and remodeling (Table 1). Extrapulmonary comorbidities including metabolic disorders have been well recognized; yet, not fully understood (11). Current pathogenetic theories assume an interplay between systemic diffusion of local inflammation and consequences of age-related comorbid conditions which impact the lungs (11).

Osteoporosis represents the most frequent metabolic comorbidity of COPD (18). Bone disease occurs in 35.1% (range: 9–69%) of patients with COPD (15). Epidemiological studies showed a twofold increased risk of osteoporosis in patients with COPD compared with controls (19). Risk factors for developing osteoporosis in COPD are due to age, low body mass index, corticosteroid use, hypogonadism, or COPD-specific reasons (20). The latters include COPD functional stage, respiratory failure, severity of dyspnea, and COPD phenotype as determined by computed tomography scan (emphysematous versus non-emphysematous) (20). From a therapeutic point of view, it is unknown whether

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**TABLE 1 | Studies reporting prevalence of metabolic comorbidities in patients with chronic obstructive pulmonary disease (COPD).**

| Comorbidity       | Prevalence | Prevalence in general population | Reference                      |
|-------------------|------------|---------------------------------|--------------------------------|
| Diabetes mellitus | 10–18.7%   | 7–11.4%                         | Dursunoglu et al. (1), Framingham Heart Study Walter et al. (12), Laghi et al. (13) |
| Dyslipidemia      | 48.3%      | 18–46%                          | CONSISTE (14)                   |
| Osteoporosis      | 35.1% (9–69%) | 5%                             | Graat-Verboom et al. (15) |
| Thyroid diseases  | 21.2% (hypothyroidism) | 7.1% (hypothyroidism) | Terzano et al. (16, 17) |
|                   | 32.2% (hyperthyroidism) | 1.3–5% (hyperthyroidism)       |                                 |
management of osteoporosis may exert a beneficial effect on disease outcome and thus prospective studies are sorely needed (21).

Metabolic syndrome is a complex disorder recognized clinically by the findings of abdominal obesity, elevated triglycerides, atherogenic dyslipidemia, elevated blood pressure, and high blood glucose and/or insulin resistance. The metabolic syndrome is frequently encountered in patients with COPD in the context of coexisting systemic inflammation (6, 21–23). Prevalence of diabetes in COPD ranges between 10 and 18.7% (12, 13, 24). A study enrolling 103,614 women showed that patients with COPD had a 1.8 relative risk of diabetes development (25). An association between diabetes and impaired lung function has also been shown (13, 26–28). A plethora of pathogenetic commonalities between COPD and diabetes have been proposed; yet, data are still scarce (25). Spill over of reactive oxygen species and pro-inflammatory mediators (IL1, IL6, TNFa, NF-kB, leptin, adiponectin, and resistin) into the circulation may lead to insulin resistance, chronic hyperglycemia, and increased lung collagen synthesis and deposition mediated by higher levels of advanced glycation products (29).

Chronic exogenous administration of corticosteroids may further affect the glycemic status through decreased insulin production and increased insulin resistance due to increased muscle catabolism, lipolysis, and free fatty acids and thus enhance the vicious cycle of COPD, systemic inflammation, and dysglycemia (25, 30). Co-existing obesity may also contribute to insulin resistance as well as systemic inflammation through release of several pro-inflammatory mediators into the circulation, and thus perpetuate both local and systemic inflammation (29).

Abnormalities in lipoprotein metabolism have been associated with COPD (6); yet, relative mechanistic data are still scarce. A recent study reported dyslipidemia in 48.3% of patients with COPD and 31.7% of controls (14). The therapeutic criterion that statins are responsible for the reduction in death rate of patients with COPD by 36% highlights the interrelationship between COPD and dyslipidemia (31). Pleiotropic effects of statins such as anti-inflammatory and immunomodulatory properties should be further investigated in this setting (32).

The interest in the role of thyroid dysfunctions in patients with COPD has been recently revived (16, 17). Compelling evidence suggested that several characteristics of patients with COPD could potentially increase the risk of developing hypothyroidism or hyperthyroidism (33, 34). In particular, severity of airway obstruction, hypoxemia, and systemic inflammation might lead to subclinical hypothyroidism or overt hyperthyroidism (35). Hyperthyroidism has been associated with reduced respiratory muscle function, exercise capacity, and enhanced risk for sleep disordered breathing leading to inspiratory and expiratory weakness in patients with COPD (36). This weakness might be attributed to decreased expression of myosin heavy chains, phrenic nerve neuropathy, or decreased neuromuscular transmission (37). Hyperthyroidism has been also associated with impaired respiratory muscle function and exercise capacity in patients with COPD (36). Importantly, the reported substantial decrease of oxygen levels accompanied by carbon dioxide retention necessitates the evaluation of whether restoration of physiologic thyroid signaling may exert therapeutic effects on patients with COPD (16).

### METABOLIC DISORDERS AND ASTHMA

Asthma is among the most common chronic diseases worldwide (Table 2). The disease is poorly controlled despite available therapeutic regimens in a substantial minority of patients (38). Among factors impairing control of symptoms and treatment response are comorbid conditions including metabolic disorders (39, 40).

Recent evidence showed that the most common metabolic dysfunction was dyslipidemia, which occurred in 18.4% of asthmatic patients, while both types of diabetes mellitus—type 1 and 2—occurred in 8.44% of patients with asthma (39). A link between metabolic syndrome and functional indices of patients with asthma has been established both in children and young adults (46–49). Asthmatic children were more likely to have elevated triglycerides and acanthosis nigricans, a marker of insulin resistance leading to diabetes (49). Metabolic syndrome-induced lung impairment in asthma could be explained by the suppression in the complex effects of insulin and insulin receptors on the lung and the airways (50); however, the exact mechanism by which these receptors could affect the developing lung remains elusive (46). Circulating levels of fatty acids and the lipotoxic state inducing innate immune responses via multiple inflammatory mechanisms, such as pattern recognition receptor activation or intracellular signaling pathways might represent a link between asthma and dyslipidemia; yet, data are still scarce (47, 51).

Abdominal obesity, another key feature of metabolic syndrome, has been associated with lung function impairment in asthma (47). The incidence of asthma almost doubled in obese subjects, while obesity represented a risk factor for severe asthma (41, 52). Experimental data showed that obese patients with asthma had a higher expression of inflammatory markers and adipokines in visceral fat, and thus adipokine dysregulation was suggested as a possible mechanism leading to obesity-mediated airway changes in asthma (53, 54).

Osteoporosis has been linked with asthma as well, mainly due to chronic corticosteroid therapy (55–57); yet musculoskeletal complications of inhaled corticosteroids are highly debatable (55, 58). Lower bone mineral density in adult asthmatic patients using inhaled glucocorticoids compared to untreated controls has been described (57, 59, 60), even though this finding was not

| Table 2 | Studies reporting prevalence of metabolic comorbidities in patients with asthma. |
|---------|---------------------------------------------------------------------------------|

| Comorbidity                      | Prevalence | Prevalence in general population | Reference |
|----------------------------------|------------|---------------------------------|-----------|
| Dyslipidemia                     | 18.38%     | 18% (age matched)               | Heck et al. (39) |
| Diabetes mellitus                | 8.44%      | 7–11.4%                         | Heck et al. (39) |
| Abdominal obesity (severe asthma)| 31% (children) 58% (adolescents–adults) | 33.4–43.3% | Schatz et al. (41), Aranceta-Bartrina et al. (42) |
| Vitamin D deficiency             | 53.3% (children) 17% (adults) | 41.6% | Chiellini et al. (43), Devreux et al. (44), Forrest et al. (45) |
uniform (61, 62). A dose response relationship between use of oral glucocorticoids with risk of fracture in patients and asthma has been extensively validated (55, 63).

An epidemiologic and mechanistic interplay between vitamin D deficiency and asthma exacerbations has been reported (38, 64). Decreased levels of serum 25-hydroxyvitamin D were associated with increased prevalence and rates of hospitalization along with reduced lung function and increased airway hyperresponsiveness in asthmatic children (44, 65). Studies found that the prevalence of vitamin D deficiency was 53.3% among asthmatic children and 17% among asthmatic adults, respectively (43, 44). Other studies showed no differences in the mean vitamin D levels between asthmatics and healthy controls, while vitamin-D deficiency was strongly associated with sputum eosinophilia, higher levels of exhaled nitric-oxide, and lung function impairment. These evidence indicate that low vitamin D levels may potentially contribute to asthma exacerbation in those patients already susceptible to disease development (66). Vitamin D deficiency has been mechanistically linked with exaggerated airway smooth muscle contractility, particularly in cases of steroid-refractory asthma and asthma exacerbations (67). A potential anti-inflammatory role of vitamin D, a steroid hormone, has also been suggested through suppression of the Th2 immunologic response (65).

To this end, supplementation therapeutic strategies have been applied in large cohorts of asthmatic patients with encouraging results (68–70). A recent Cochrane meta-analysis of seven trials including 435 children, and two studies including 658 adults stated that oral vitamin D supplement reduced the risk of severe asthma exacerbations requiring hospitalization from 6% in the control group to 3% in the treatment arm (71). Despite promising therapeutic efficacy there is much to be learned, given that the aforementioned data mainly arise from just three trials and it is currently unknown whether this therapeutic effect can be expanded to all asthmatic patients or in those with low baseline levels of vitamin D.

**METABOLIC DISORDERS AND ILDs**

Interstitial lung diseases constitute a group of diffuse parenchymal lung disorders, associated with substantial morbidity and mortality (72–76) (Table 3). Idiopathic pulmonary fibrosis (IPF) and sarcoidosis are among the most common ILDs (77, 78). The role of metabolic disorders in ILDs has been recently revived leading to studies investigating possible therapeutic targets for patients with ILDs (4, 79, 80).

Diabetes mellitus represent the most frequently encountered endocrine comorbidity in patients with IPF (4, 79, 90–93). The prevalence of diabetes in patients with IPF ranged from 10 to 39% (81–83). A potential association between IPF and diabetes could be attributed to complications from chronic corticosteroid therapy (81, 82, 94). The impact of diabetes on disease mortality still remains elusive and controversial (82, 95, 96).

Thyroid disorders have been recently implicated as common comorbid conditions in patients with IPF (4, 80, 93, 97–99). Two recent studies demonstrated higher prevalence of hypothyroidism among patients with IPF (16.8% of subjects with IPF and 7.1% of control subjects). Interestingly, 13% of men and 28% of women were affected (86, 93). An interesting observation was that presence of hypothyroidism was associated with worse outcomes in patients with IPF (86). Interestingly, our study group identified that type 2 iodothyronine deiodinase (DIO2), the enzyme that converts T4 to active T3, was upregulated in the lungs of patients with IPF and particularly in alveolar epithelial cells, the metabolically active cells of the lung (100). DIO2 induction potentially reflected a compensatory response in order to boost local conversion of T4 to T3 to enhance the metabolic state of alveolar epithelial cells under stress conditions, considering that DIO2 knockout mice exhibited enhanced fibrotic responses to bleomycin. Intriguingly, experimental data showed that aerosolized thyroid hormone administration exerted anti-fibrotic effects in two experimental models of lung fibrosis through a mechanism that involved improved mitochondrial function and mitophagy (100). Same results were observed with sobetamide, a thyroid-mimetic agent that acts through activation of thyroid hormone signaling by selective binding to thyroid hormone receptor (100). Further studies exploring the effect of thyroid hormone administration in patients with IPF are greatly anticipated.

With regard to dyslipidemia, the reported prevalence in patients with IPF ranges between 11 and 21.7% (84, 85). Interestingly, Enomoto et al. recorded dyslipidemia in 19.2% of patients with IPF and 46% in the control group (82). The exact role of dyslipidemia, elevated levels of fatty acids, and oxidative stress via nicotinamide adenine dinucleotide phosphate oxidase activation in the pathogenesis of pulmonary fibrosis remains to be addressed (101).

Sarcoidosis is a multisystem inflammatory disease characterized by the presence of non-caseating granulomas in the affected organs (102–104). Lungs are affected in more than 90% of patients with sarcoidosis (104, 105). Data on the impact of metabolic disorders in chronic lung diseases

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**Table 3**

| Comorbidity          | Prevalence   | Prevalence in general population | Reference                      |
|----------------------|--------------|---------------------------------|--------------------------------|
| IPF                  |              |                                 |                                |
| Diabetes mellitus    | 10–39%       | 11.4%                           | British study (81), Japanese study (82), American study (83) |
| Dyslipidemia         | 11–21.7%     | 18–46%                          | Enomoto et al. (82), Kaddah et al. (84), Sherbini et al. (85) |
| Hypothyroidism       | 16.8% (13% men, 28% women) | 7.1%                           | Oldham et al. (88) |
| Sarcoidosis          |              |                                 |                                |
| Thyroid diseases     | 13.1%        | 4%                              | Nowinski et al. (87) |
| Diabetes mellitus    | 7.4%         | 7%                              | Nowinski et al. (87) |
| Osteoporosis         | 5.7%         | 5%                              | Nowinski et al. (87) |
| Hypercalcemia        | 10–15%       | 2%                              | Saidenberg-Kermaniach et al. (88), Press et al. (89) |

ILDs, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis.
comorbidities in sarcoidosis is limited and have mainly focused on calcium metabolism (87). In particular, 13.1% of patients with sarcoidosis were also diagnosed with thyroid diseases, 7.4% with diabetes, and 5.7% with osteoporosis, respectively (87). Age and multiorgan involvement of sarcoidosis represented risk factors for metabolic comorbidities (106). Finally, a case-control study of 111 patients with sarcoidosis suggested a potential association between autoimmune thyroid disorders and sarcoidosis (107, 108).

Hypercalcemia and hypercalcuria occur in a small, but significant number of patients with sarcoidosis, but if present, they constitute indication for treatment (103, 109, 110). Although earlier studies reported that hypercalcemia was present in 2–63% of patients with sarcoidosis, recent data show that the true prevalence is between 10 and 15% (88). Increased activity of the 1-alpha hydroxylase enzyme of tissue macrophages has been suggested to have a crucial role for the elevation of levels of 1,25-dihydroxyvitamin D3 (calcitriol), the hormonally active metabolite of vitamin D, which is responsible for hypercalcemia (111, 112). Bell et al. were the first to demonstrate elevated serum calcitriol levels in patients with sarcoid hypercalcemia (112). Since then, our understanding for the ideal therapeutic management of hypercalcemia associated with sarcoidosis has been significantly increased (113). Glucocorticoids have been used as first-line therapy in the management of hypercalcemia associated with sarcoidosis; yet with major complications that should be treated cautiously. Steroid-sparing agents including azathioprine and methotrexate have widely used in advanced disease stages or steroid-refractory cases with controversial results (113, 114). Finally, the investigation of the role of biphosphonates and especially zoledronic acid in sarcoid hypercalcemia is currently under investigation (113, 115).

**METABOLOMICS IN CHRONIC LUNG DISEASES**

For the past few years, the field of cellular bioenergetics and metabolism and their implication in the pathogenesis of chronic lung diseases has received much of attention. The term “metabolomics” refers to the systematic investigation of metabolic pathways (metabolome) and biochemical compounds created in a living system, called metabolites at a specific timepoint (116). Currently, quantification of metabolites of a biological system is performed by two techniques: mass spectrometry and nuclear magnetic resonance spectroscopy (NMR) (116). Urine, plasma, and lung tissue represent excellent biological specimens to study metabolomics with urine being the most promising one, because of its ease of collection, low cell, and protein content and rich chemical composition (117). Exhaled breath condensate is an easily accessible biomarker tool to study metabolome of the airway lining fluid, yet it presents with major limitations, since it is affected by several confounding factors, such as age, sex, smoking, temperature, humidity, and oral cavity contamination (117). Preliminary studies have shown that urine metabolomics profile could be used as reliable biomarker to diagnose heterogeneous syndromes with complex underlying pathogenesis, such as asthma (118) and COPD (117), and most importantly to differentiate asthma from COPD based on their metabolomic profile (119). Exhaled breath condensate leukotrienes have been used to distinguish asthmatic patients from controls (120). COPD patients exhibit abnormal muscular bioenergetics (121) and impaired microbiome-related metabolites (122) as indicated by increased plasma levels of branched-chain amino acids and urinary levels of hippurate and formate, respectively. Metabolomics profile has been also used to distinguish COPD patients with different phenotypes based on severity of functional impairment and the presence of emphysema and cachexia (123). Disrupted glycolysis, enhanced fatty acid accumulation, increased lactic acid, and lactate dehydrogenase production, as well as haem degradation have been identified as major events of impaired mitochondrial metabolism in both IPF and COPD patients (124–127). In addition, IPF lungs showed disrupted glutathione synthesizing pathway and consequently increased oxidant burden. Increased formation of proline, a key substrate for collagen biosynthesis, from ornithine through activation of ornithine aminotransferase has been also shown in IPF lungs (126). Interestingly, increased levels of ornithine aminotransferase have been negatively correlated with functional indices of disease severity including FVC (126). Intermediate metabolites of glycolysis including lactic acid have been shown to activate the TGF-β pathway inducing myofibroblast differentiation (127). Glycolytic reprogramming, a form of Warburg effect seen in cancer cells, has been recently implicated in fibroblasts to myofibroblasts differentiation. Inhibition of glycolysis exerted therapeutic effects in experimental lung fibrosis, highlighting a novel therapeutic area by shifting the metabolic requirements of key cellular components toward oxidative phosphorylation (128). The role of impaired mitochondrial metabolism in the pathogenesis of lung fibrosis has been recently demonstrated by a study showing that IPF lungs exhibit alveolar epithelial cells with damaged and dysfunctional mitochondria due to downregulated levels of PINK1, the master transcription factor of mitophagy (129). The cardinal role of mitochondrial metabolism in alveolar epithelial cell apoptosis in the context of lung fibrosis has been also highlighted by a recent publication from our study group showing therapeutic effects of aerosolized hormone administration in experimental lung fibrosis through enhancement of mitochondrial bioenergetics, as reported above (100). Interestingly, the concept of impaired mitophagy-mediated lung fibrosis has been recently suggested for lung macrophages and fibroblasts; yet, on a cell-specific manner (130–132). The above findings have also proven given human relevance, that products of fibroblasts' mitochondrial metabolism including mitochondrial DNA (mtDNA) have been recently shown to serve as prognosticators of IPF mortality (133). The above preclinical studies highlight the importance of therapeutic restoration of the disrupted metabolome and the use of circulating metabolites as biomarkers of disease prognosis and treatment response.

**FUTURE PERSPECTIVES AND CONCLUDING REMARKS**

There is increasing evidence that ameliorating the metabolic profile of a subgroup of patients with chronic lung diseases...
could have an impact on disease clinical course. To this end, extensive monitoring of metabolic alterations involving glucose metabolism, lipids and thyroid hormones signaling, calcium, and vitamin-D should be implemented in the everyday clinical practice of patients with chronic lung diseases. The exact role of vitamin D in patients with chronic lung diseases and its role in disease management remain to be addressed. In view of the current disappointing status of the therapeutic compounds targeting the extracellular matrix (90), novel drug discoveries aim to protect the epithelium or disrupt myofibroblast differentiation through restoration of physiologic cellular metabolism. Studies on the role of aerosolized thyroid hormone administration in patients with IPF are greatly anticipated. In the, not so distant, future metabolomics could represent the missing line that will connect the dots of translational research to the clinical setting. The idea of investigating the metabolic profile to stratify patients based on disease prognosis and treatment response has been applied in diabetes mellitus or hyperlipidemia for decades. In parallel with smoking and physical activity, diet is an important contributor for prevention of disease development and progression. Ultimately, the clinical judgment will still prevail, but molecular tools can complement clinical criteria. Similarly, to what is happening in diabetes, dyslipidemia, liver, and renal diseases, specific nutritional regimens based on the patient’s metabolomic profile may exert a beneficial impact on disease progression and mortality in chronic lung diseases. Cellular metabolism is too precious to be underestimated.

**AUTHOR CONTRIBUTIONS**

OP wrote the manuscript along with TK. The manuscript was supervised and significantly modified by AT. All authors offered intellectual contribution and approved the manuscript.

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