Diabetes Management

Type 2 diabetes mellitus and chronic obstructive pulmonary disease: need for a double-pronged approach

"...pulmonary function is reduced in people with diabetes mellitus and ... diabetes mellitus is a common 'comorbidity' in people with chronic obstructive pulmonary disease."

Gregory L Kinney*[1] & Emma H Baker[2]

Epidemiologists occasionally find themselves having to bridge fields that are not typically related and the intersection of diabetes mellitus and chronic lung disease may be one of these areas. Epidemiologists have commented since the early 1970s that pulmonary function is reduced in people with diabetes mellitus and, more recently, that diabetes mellitus is a common 'comorbidity' in people with chronic obstructive pulmonary disease (COPD). Despite this, endocrinologists rarely measure lung function and pulmonologists are unlikely to order laboratory tests of fasting glucose or glycated hemoglobin.

Type 2 diabetes mellitus and COPD are both common and increasing in prevalence. The age-adjusted prevalence of Type 2 diabetes increased in the USA between 1980 and 2011 from 2.8 to 6.4% and incidence has followed this trend, increasing from 3.5/1000 to 7.7/1000 [1]. The National Health and Nutrition Examination Survey indicated that 13.5% of the adult population have airflow obstruction on spirometry that meets diagnostic criteria for COPD [2]. Between 1990 and 2020, COPD is projected to move from the sixth to third most common cause of death and fourth to third most common cause of morbidity worldwide [3]. Although both conditions are common in older adults, they coexist more frequently than expected by chance. People with diabetes mellitus have a 22% increased risk of developing COPD [4], whereas those with COPD have a 40–100% increased risk of developing diabetes [5].

The strong relationship between these two conditions is due to multiple interrelated mechanisms, including shared risk factors, direct causation and treatment effects. Cigarette smoking is the primary cause of COPD. Cigarette smoking also increases insulin resistance [6] and cigarette smokers are 30–40% more likely to develop Type 2 diabetes than nonsmokers [7].

Diabetes mellitus is associated with reduced pulmonary function. This has been shown in a variety of settings,

KEYWORDS
• chronic obstructive pulmonary disease • COPD • exacerbation • glycemic control • infection • Type 2 diabetes mellitus

"People with diabetes mellitus have a 22% increased risk of developing chronic obstructive pulmonary disease, whereas those with chronic obstructive pulmonary disease have a 40–100% increased risk of developing diabetes."

[1]Colorado School of Public Health, Department of Epidemiology, University of Colorado, Anschutz Medical Campus, 13001 East 17th Avenue, Room W3135, Aurora, CO 80045, USA
[2]Institute of Infection & Immunity, St George's, University of London, London, UK
*Author for correspondence: greg.kinney@ucdenver.edu

Future Medicine part of fsg

including inhaled insulin trials and research into microvascular complications affecting various organ systems, and this reduction persists across categories of COPD severity [8]. Researchers have noted that hyperglycemia and inflammation inherent in diabetes have small effects on the lungs, likely caused by accumulation of damage across a variety of pathways, which may account for observed abnormalities in pulmonary function. Reduced lung elasticity and total lung volume may be accounted for by advanced glycation end product-related crosslinking of collagen and elastin. Reduced gas transfer may be attributable to microvascular disease affecting pulmonary capillaries. Chronic inflammation, increased propensity for lung infection and phrenic nerve neuropathy impairing diaphragmatic function are also likely to contribute to a reduction in lung function.

COPD patients have increased oxidative stress, systemic inflammation and hypoxia, all of which increase insulin resistance and could contribute to the development of Type 2 diabetes. These pathologies are enhanced during COPD exacerbations, when they may contribute to the high prevalence of acute hyperglycemia [9]. In COPD, progressive breathlessness leads to reduced physical activity and obesity, both of which are well-recognized risk factors for Type 2 diabetes mellitus. Treatment of COPD with regular high-dose inhaled corticosteroids is associated with a 34% increased risk of developing diabetes [10]. Repeated short courses of oral corticosteroids for exacerbations may also contribute to insulin resistance.

"Endocrinologists and pulmonologists should be aware of other conditions that commonly coexist with Type 2 diabetes mellitus and chronic obstructive pulmonary disease. This may necessitate a 'multipronged' rather than merely a 'dual-pronged' approach."

Type 2 diabetes mellitus and COPD share an insidious onset, which classically leads to late presentation and underdiagnosis. In the USA it is estimated that approximately half of people with Type 2 diabetes are undiagnosed [11] and two-thirds of people with low lung function have no prior diagnosis of obstructive lung disease [12]. Recognition of diabetes or COPD may be even more difficult in people already diagnosed with the other condition, particularly where they are seen by an organ-based specialist. Patients with diabetes developing pulmonary damage may simply exercise a little less, complain occasionally of breathlessness on exertion and experience seasonal upper respiratory tract infections a little more often and a little more severely. All of these symptoms might be attributed by endocrinologists to hyperglycemia, treatment of diabetes and lifestyle. Patients with COPD developing diabetes may experience more frequent exacerbations, reduced exercise tolerance and impaired health status, which are more likely to be ascribed by pulmonologists to deteriorating lung disease than to concomitant diabetes.

So, should routine clinical work up include measurement of pulmonary function for people with diabetes and glucose tolerance for people with COPD? In the general population, routine screening for these chronic diseases is not currently recommended [13,14]. Instead, targeted assessment of symptomatic or high-risk patients should be considered. Using this approach, lung function testing would be indicated for patients with diabetes who have a significant pack year smoking history (>10 pack years) with respiratory symptoms, recurrent respiratory infections or reduced exercise tolerance. As COPD patients are at high risk of diabetes, we propose that they should all undergo assessment of glucose tolerance.

Systematic identification of comorbidities is only worthwhile if it has potential to improve patient outcomes. People with both diabetes and COPD have worse clinical outcomes than patients with either condition alone. People with diabetes are 27% more likely to die from COPD than people without diabetes [15]. People with COPD who have concomitant diabetes mellitus have a 70% increased 3-year [16] and 300% increased 10-year mortality [17]. Diabetes and COPD have synergistic effects on morbidity, together producing a greater decline in health status, reduction in exercise tolerance and increase in hospitalizations than either separately.

Where diabetes mellitus and COPD coexist, a dual-pronged approach to management has potential to improve control and delay progression of both diseases, with synergistic benefits for health. For people with diabetes, treatment of coexisting airways disease can reduce breathlessness, facilitating increased physical activity and weight control. Respiratory-focused measures, including smoking cessation, influenza vaccination, prompt antibiotic treatment for respiratory infection and long-acting bronchodilators to reduce exacerbation rate, may reduce oxidative stress and systemic inflammation, reducing insulin resistance and helping to control diabetes. For people with COPD, endocrine-focused measures, particularly blood

glucose control, may reduce systemic inflammation and respiratory infection, with beneficial effects on exacerbation rate and disease progression. Use of the minimum effective dose of inhaled and oral corticosteroids should be practiced to avoid exacerbating diabetes mellitus and precipitating diabetic complications [18]. Drugs for diabetes may have 'off-target' benefits for airways disease. In addition to blood glucose-lowering effects, metformin has anti-inflammatory and antioxidant actions that could reduce pulmonary inflammation in COPD. In two small studies, one retrospective [19] and one open label [20], metformin treatment was associated with an improvement in lung function [19] and respiratory muscle strength [20] in people with COPD and diabetes mellitus. These findings now need to be confirmed in prospective, randomized, placebo-controlled trials.

A recent paper [21], accompanied by an excellent editorial, described COPD and its comorbidities (including diabetes) as multimorbidities. This new term was coined to encompass the diverse linked diseases experienced by the study population that appear to be driven by common smoking behaviors and lack of physical activity. Patients with multimorbidities are likely to present to the specialist with expertise in the condition that first becomes symptomatic. Endocrinologists and pulmonologists should be aware of other conditions that commonly coexist with Type 2 diabetes mellitus and COPD. This may necessitate a 'multipronged' rather than merely a 'dual-pronged' approach.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Centers for Disease Control, Diabetes Public Health Resource, National Surveillance. www.cdc.gov/diabetes/statistics/prev/national/figage.htm

2 Ford ES, Mannino DM, Wheaton AG, Giles WH, Presley-Cantrell L, Croft JB. Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: findings from the national health and nutrition examination surveys from 1988–1994 to 2007–2010. *Chest* 143, 1395–1406 (2013).

3 Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. *Lancet* 349, 1498–1504 (1997).

4 Ehrlich SF, Quesenberry CP Jr, Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. *Diabetes Care* 33, 55–60 (2010).

5 Wells CE, Baker EH. Metabolic syndrome and diabetes mellitus in COPD. *Eur. Respir. Mon.* 59, 117–134 (2013).

6 Attvall S, Fowelin J, Lager I, Von Schenck H, Smith U. Smoking induces insulin resistance – a potential link with the insulin resistance syndrome. *J. Intern. Med.* 233, 327–332 (1993).

7 US Department of Health and Human Services. The health consequences of smoking – 50 years of progress: a report of the surgeon general. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014. www.surgeongeneral.gov/library/reports/50-years-of-progress/

8 Kinney GL, Black-Shinn JL, Wan ES *et al.* COPD Gene Investigators. Pulmonary function reduction in diabetes with and without chronic obstructive pulmonary disease. *Diabetes Care* 37, 389–395 (2014).

9 Baker EH, Janaway CH, Philips BJ *et al.* Hyperglycaemia is associated with poor outcomes in people admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax* 61, 284–289 (2006).

10 Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *Am. J. Med.* 123, 1001–1006 (2010).

11 McKinlay J, Marceau L. US public health and the 21st century: diabetes mellitus. *Lancet* 356, 757–761 (2000).

12 Mannino DM, Gagnon RC, Petty TL *et al.* Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988 – 1994. *Arch. Intern. Med.* 160, 1683–1689 (2000).

13 Pottie K, Jaramillo A, Lewin G *et al.* Canadian Task Force on Preventive Health Care. Recommendations on screening for Type 2 diabetes in adults. *CMAJ* 184, 1687–1696 (2012).

14 US Preventive Services Task Force. Screening for chronic obstructive pulmonary disease using spirometry. www.uspreventiveservicestaskforce.org/uspstf08/copd/copdrs.htm

15 Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S *et al.* Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N. Engl. J. Med.* 364, 829–841 (2011)

16 Miller J, Edwards LD, Agustí A *et al.;* Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. *Respir. Med.* 107, 1376–1384 (2013).

17 Gudmundsson G, Ulrik CS, Gislason T *et al.* Long-term survival in patients hospitalized for chronic obstructive pulmonary disease: a prospective observational study in the Nordic countries. *Int. J. Chron. Obstruct. Pulmon. Dis.* 7, 571–576 (2012).

18 Caughey GE, Preiss AK, Vitry AI, Gilbert AL, Roughead EE. Comorbid diabetes and COPD: impact of corticosteroid use on diabetes complications. *Diabetes Care* 36, 3009–3014 (2013).

19 Kim HJ, Lee JY, Jung HS *et al.* The impact of insulin sensitisers on lung function in patients with chronic obstructive pulmonary disease and diabetes. *Int. J. Tuberc. Lung Dis.* 14, 362–367 (2010).

20 Sexton P, Metcalf P, Kolbe J. Respiratory effects of insulin sensitisation with metformin: a prospective observational study. *COPD* 11, 133–142 (2014).

21 Van Remoortel H, Hornikx M, Langer D *et al.* Risk factors and comorbidities in the preclinical stages of chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 189, 30–38 (2014).