6. Lal C, Hardiman G, Kumbhare S, Strange C. Proteomic biomarkers of cognitive impairment in obstructive sleep apnea syndrome. *Sleep Breath* [online ahead of print] 2 Jul 2018; DOI: 10.1007/s11325-018-1693-8.

Reply to Kawada

From the Authors:

After the publication of our review (1), Dr. Kawada raised important comments in a letter to the editor, highlighting that serum insulin and insulin activity in the brain could play a role in the relationship between obstructive sleep apnea (OSA) and cognitive decline. OSA has been associated with a higher risk of insulin resistance (IR) and type II diabetes mellitus (T2DM) (2) in studies that included mostly middle-aged subjects. IR occurs when tissues do not respond effectively to insulin, and thus higher levels are required to keep blood glucose levels normal. When an individual cannot keep up with this increased endogenous insulin production/secretion, glucose levels start to rise and diabetes ensues. Many potential mechanisms have been proposed to explain this relationship between OSA and IR/T2DM. Intermittent hypoxemia and sleep fragmentation caused by OSA lead to inflammation, oxidative stress, and increased sympathetic nervous system activity (2), all of which have the potential to increase IR and lead to T2DM (2). OSA may play a causal role in the pathophysiology of IR/T2DM, as insulin sensitivity was reported to be improved by a treatment for OSA (continuous positive airway pressure therapy) (2), although not all studies have shown that effect. In middle-aged individuals compared with the elderly, OSA is more strongly associated with metabolic syndrome, a condition characterized by central obesity, hypertension, dyslipidemia, and impairments in glucose control, including IR (3). Therefore, it is important to consider the effects of OSA in middle age versus late life on metabolic, vascular, and cognitive outcomes.

Altered cerebral insulin activity can be observed when there is IR in the brain, or when insulin transporters at the blood–brain barrier are downregulated as a result of the compensatory hyperinsulinemia that follows peripheral IR (4). Altered insulin activity has been hypothesized to affect cognitive health. In addition to its role in glucose metabolism, insulin is involved in a signal transduction cascade that ultimately affects synaptic plasticity (4). In fact, insulin is involved in long-term potentiation by modulating the expression of *N*-methyl-D-aspartate receptors. Moreover, insulin modulates neurotransmitter and nitric oxide levels, and thereby may play a role in vascular and cognitive functions (4). IR has been associated with cognitive deficits in both human and animal studies (4). Interestingly, in a recent meta-analysis, Cao and colleagues investigated the effects of several antidiabetic agents and concluded that these agents were associated with improved cognitive performance in patients with mild cognitive impairment or Alzheimer's disease (AD) in randomized clinical trials (5). In fact, IR/T2DM is associated with cognitive impairment, cognitive decline, and increased risk of dementia (4). However, the connection between IR and AD does not appear to involve classic AD pathology, as humans with T2DM do not show increased plaques and tangles postmortem (6). An alternative mechanism proposed for the added risk of dementia with impaired insulin function is based on the metabolic and cerebrovascular abnormalities shared by the two conditions.

In summary, although OSA is a risk factor for IR/T2DM in middle-aged individuals, which in turn could increase the risks of cognitive decline and dementia, there is currently not enough evidence to conclude that IR/T2DM might be one of the mechanisms that explain these associations. That said, OSA and IR/T2DM present similar pathological mechanisms, and thus the concomitant presence of these conditions may lead to an additive insult to the brain. However, given the interaction between OSA and IR, insulin regulation may be an interesting avenue to explore when investigating how OSA increases the risk of dementia and cognitive decline. Because OSA and IR/T2DM are treatable, clarifying these associations has the potential to lead to possible interventions to reduce or even prevent neurodegeneration; however, the current state of the literature lacks the appropriate evidence. ■

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References

1. Gosselin N, Baril AA, Osorio RS, Kaminska M, Carrier J. Obstructive sleep apnea and the risk of cognitive decline in older adults. *Am J Respir Crit Care Med* 2019;199:142–148.
2. Kent BD, McNicholas WT, Ryan S. Insulin resistance, glucose intolerance and diabetes mellitus in obstructive sleep apnoea. *J Thorac Dis* 2015;7:1343–1357.
3. Assoumou HG, Gaspoz JM, Sforza E, Pichot V, Celle S, Maudoux D, *et al*. Obstructive sleep apnea and the metabolic syndrome in an elderly healthy population: the SYNAPSE cohort. *Sleep Breath* 2012; 16:895–902.
4. Neth BJ, Craft S. Insulin resistance and Alzheimer's disease: bioenergetics linkages. *Front Aging Neurosci* 2017;9:345.
5. Cao B, Rosenblat JD, Brietzke E, Park C, Lee Y, Musial N, *et al*. Comparative efficacy and acceptability of antidiabetic agents for Alzheimer's disease and mild cognitive impairment: a systematic review and network meta-analysis. *Diabetes Obes Metab* 2018;20: 2467–2471.
6. Abner EL, Nelson PT, Kryscio RJ, Schmitt FA, Fardo DW, Woltjer RL, *et al*. Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology. *Alzheimers Dement* 2016;12:882–889.

Deconvoluting Chronic Obstructive Pulmonary Disease: Are B Cells the Frontrunners?

To the Editor:

In the era of precision medicine, the observable differences between patients with chronic obstructive pulmonary disease (COPD) are calling into question the current way of classifying subjects with COPD based solely on a measure of their lung function. Computed tomography has been instrumental in identifying COPD subphenotypes, such as airway disease (bronchiolitis) and parenchymal destruction (emphysema), the relative contribution of which varies from patient to patient (1). Emphysema is characterized by a molecular signature indicating predominant B-cell activation and lymphoid follicle (LF) formation, which is absent in bronchiolitis regardless of airflow limitation (2).

The exciting work by Ladjemi and colleagues provides a novel insight into the humoral immune pathobiology (or "endotype") in COPD (3). The study shows IgA production occurring in distal airway LFs from patients with severe COPD. This finding raises questions about the role of the distal airways in the pathogenesis and progression of COPD. Disease and loss of terminal and transitional bronchioles are present in the lungs of smokers when no emphysematous destruction is present, indicating that small airway disease may be an early pathological feature of COPD (4). The anatomic sets of distal airways associated with B cell–predominant immune responses and the timing of these responses in the pathogenesis of COPD are still unclear.

Furthermore, Ladjemi and colleagues showed that IL-21, which is crucial for the maturation of B cells into plasma cells capable of producing high-affinity antibodies against foreign antigens (5), was significantly overexpressed in the LFs at all stages of COPD. This finding is in line with previous studies showing the presence of oligoclonal or monoclonal LF B cells in the COPD lung and suggests an immune reaction that is triggered by precise antigens (6). However, because microbial diversity declines as COPD progresses (7), it will be essential to investigate the nature of the antigens that trigger B cell–driven immune responses in the severe stages of COPD, and how precisely the lung microbiome contributes to those responses.

To date, these questions remain unanswered, in large part owing to the difficulty—apart from rare cases—of obtaining repeated samplings of lung specimens from one subject longitudinally, which would allow us to track the pathobiology of COPD over time. Indeed, unlike the airway subphenotype, the emphysematous subphenotype is associated with a B cell–predominant endotype, but the temporal sequence and the extent of the overlap of these two pathologic manifestations, if any, is unknown. Thus, further studies are very much needed to clarify the nature and exact sequence of events leading from a B cell–predominant immune response to LF formation during the onset and progression of distinct COPD subphenotypes. Filling this knowledge gap will be crucial for early COPD diagnosis and intervention on the basis of the immunologic endotype involved. ■

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References

1. Bhatt SP, Washko GR, Hoffman EA, Newell JD Jr, Bodduluri S, Diaz AA, *et al*.; COPDGene Investigators. Imaging advances in chronic obstructive pulmonary disease: insights from COPDGene. *Am J Respir Crit Care Med* [online ahead of print] 10 Oct 2018; DOI: 10.1164/rccm.201807-1351SO.
2. Faner R, Cruz T, Casserras T, López-Giraldo A, Noell G, Coca I, *et al*. Network analysis of lung transcriptomics reveals a distinct B-cell signature in emphysema. *Am J Respir Crit Care Med* 2016;193: 1242–1253.
3. Ladjemi MZ, Martin C, Lecocq M, Detry B, Aboubakar Nana F, Moulin C, *et al*. Increased IgA expression in lung lymphoid follicles in severe COPD. *Am J Respir Crit Care Med* [online ahead of print] 19 Oct 2018; DOI: 10.1164/rccm.201802-0352OC.
4. Koo HK, Vasilescu DM, Booth S, Hsieh A, Katsamenis OL, Fishbane N, *et al*. Small airways disease in mild and moderate chronic obstructive pulmonary disease: a cross-sectional study. *Lancet Respir Med* 2018; 6:591–602.
5. Zotos D, Coquet JM, Zhang Y, Light A, D'Costa K, Kallies A, *et al*. IL-21 regulates germinal center B cell differentiation and proliferation through a B cell-intrinsic mechanism. *J Exp Med* 2010;207:365–378.
6. Baraldo S, Turato G, Lunardi F, Bazzan E, Schiavon M, Ferrarotti I, *et al*. Immune activation in α1-antitrypsin-deficiency emphysema: beyond the protease-antiprotease paradigm. *Am J Respir Crit Care Med* 2015; 191:402–409.

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