COMMENT ON RHEE ET AL.

Association Between Glycemic Status and the Risk of Parkinson Disease: A Nationwide Population-Based Study. Diabetes Care 2020;43:2169–2175

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Metabolic diseases, such as diabetes and obesity, increase susceptibility for additional long-term complications, including Parkinson disease (PD). Rhee et al. (1) aim to address this issue by using a large data set obtained from the Korean National Health Insurance consisting of a sample of over 15 million individuals aged 40 years and older who had undergone routine checkups between 2009 and 2010. They evaluated diabetes as a risk factor for PD by analyzing how PD risk varies according to baseline glucose tolerance status, diabetes duration, and comorbidities such as obesity, cardiovascular disease, and cerebrovascular disease. The authors demonstrate that the risk of PD is increased in patients with diabetes and that the incidence of PD is proportional to the degree of exposure to hyperglycemia. The finding that the diagnosis of diabetes itself is not enough to accurately predict PD risk along with the authors' use of a nationwide database highlight the crucial importance of better understanding the shared mechanisms between PD and diabetes. While the authors present novel information regarding risk factors for PD, their findings could be strengthened if corroborated by further insight into the underlying mechanisms that contribute to the relationship between PD and diabetes.

Both obesity and PD are associated with elevated levels of proinflammatory markers. Several studies have identified an association between increased levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and hs-CRP and obesity. Given the elevated levels of inflammatory markers observed in obese individuals, many studies have focused on categorizing obesity as a low-grade inflammatory condition (2). This low-grade inflammatory response is believed to contribute to a heightened risk of obesity-associated diseases such as diabetes. The increase in levels of proinflammatory markers is not limited to metabolic diseases but also extends to neurological conditions. Notably, the striatum of deceased PD patients exhibits increased levels of inflammatory mediators such as interferon-γ (IFN-γ), IL-1β, IL-2, IL-3, IL-10, macrophage migration inhibitory factor, and TNF-α. The risk of developing PD has also been shown to decrease in response to anti-inflammatory drugs (3).

The cholinergic agonist nicotine also exhibits anti-inflammatory properties and can modulate the physiological effects of obesity and diabetes. Nicotine activates the anti-inflammatory cholinergic pathway by acting on the α7 nicotinic acetylcholine receptor (α7nAChR). Nicotinic acetylcholine receptor (nAChR) agonists are effective at inhibiting the inflammatory response and the production of proinflammatory markers. Treatment with nAChR agonists modulates the production of proinflammatory cytokines from immune cells. In addition to low-grade inflammation, the metabolic dysfunction of obesity is characterized by insulin resistance, which itself is reduced by nicotine. In obesity, the proinflammatory effects of cytokines primarily involve the nuclear factor-κB (NF-κB) and c-Jun N-terminal kinase intracellular signaling pathways. By activating α7nAChR in patients with obesity, NF-κB is prevented from nuclear entry, which results in improved insulin sensitivity (4). The levels of IL-12, IL-1, TNF-α, and IFN-γ are also increased in diabetes and thus attenuated by nicotine. Finally, electrical stimulation of the vagus nerve inhibits TNF synthesis in wild-type mice but not in α7-deficient mice, highlighting the essential role of α7nAChR in inhibiting cytokine synthesis via the cholinergic anti-inflammatory pathway (5).

In patients with PD, the dysfunctional striatal dopaminergic neurons are stimulated by nicotine (6). Furthermore, tobacco use is negatively correlated with the development of PD. In a longitudinal study spanning 65 years with a sample of 30,000 individuals, there was a negative correlation between smoking and the development of PD (7). Given that Rhee et al. have access to such a large data set, it would be worthwhile to explore the interaction between smoking and the incidence of PD. This could help elucidate the relationship between PD and diabetes by determining if

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smoking has an effect on a patient with diabetes developing PD. It is imperative to develop a selective cholinergic agonist that is not addictive and does not expose an individual to the adverse physiologic effects associated with smoking. Novel pharmaceutical interventions that specifically target the cholinergic pathway could yield improved long-term treatment outcomes for patients with PD and diabetes.

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