COMMENT ON NEELAND ET AL.

The Impact of Empagliflozin on Obstructive Sleep Apnea and Cardiovascular and Renal Outcomes: An Exploratory Analysis of the EMPA-REG OUTCOME Trial. Diabetes Care 2020;43:3007–3015

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We read with great interest the leading article by Neeland et al. (1) highlighting the beneficial effects of empagliflozin treatment on several metabolic end points among participants with type 2 diabetes and obstructive sleep apnea (OSA) in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME). In addition, the authors observed a lower frequency of new-onset OSA, even when adjusting for baseline BMI. The authors provided few physiological explanations for the favorable effects of empagliflozin, mainly attributing them to the diuretic and natriuretic effects of the drug. Among the latter effects were *1*) reduction of intrathoracic fluid retention and rostral fluid shifts from the legs and *2*) interrupted sleep cycles and decreased rapid eye movement sleep secondary to nocturia.

We would like to suggest another explanation for the lower frequency of new-onset OSA in patients in the empagliflozin group. In a previous work (2), we hypothesized that sodium–glucose cotransporter 2 inhibitors (SGLT2i) might be therapeutically beneficial for patients with respiratory diseases and carbon dioxide (CO_2) retention (e.g., with OSA and with obesity hypoventilation syndrome [OHS]). OHS is a common pulmonary disease, defined by the presence of obesity (BMI >30 kg/m^2) associated with daytime hypercapnia (pCO_2 >45 mmHg) in the absence of other causes of hypoventilation. Approximately 70–90% of patients with OHS also have OSA.

In these patients, CO_2 removal is reduced due to limited ventilation, causing chronic hypercapnia and hypoxemia (due to obligatory reduction in alveolar oxygen pressure, secondary to the increase in alveolar CO_2 pressure). The combination of chronic hypoxemia and hypercapnia induces pulmonary vaso-constriction, sympathetic activation, and increase in serum catecholamine level (3), all of which could eventually contribute to development of systemic and pulmonary hypertension.

It is important to segment the issue of CO_2 retention (hypercapnia) into endogenous CO_2 production and limited CO_2 removal. It is hypothesized that SGLT2i reduce the endogenous production of CO_2. SGLT2i force glucose diuresis and reduce the availability of glucose as an energy substrate for body cell metabolism. Assuming that total body energy expenditure remains constant and less glucose is available as substrate, other substrates must be utilized. Thus, SGLT2i medication potentially facilitates a preferential use of lipids (or proteins) as energy source for metabolism (for a given amount of oxygen consumed, more CO_2 is produced from the metabolism of carbohydrates compared with that of lipids or proteins). Had such a shift in energy substrate occurred, less endogenous CO_2 production would be expected, with less CO_2 to be removed by the respiratory system.

By doing so, SGLT2i decrease endogenous CO_2 production and could potentially prevent the complications of hypercapnia. In addition to having other well-documented therapeutic effects, SGLT2i might even change the natural course of respiratory diseases with CO_2 retention (OSA and OHS).

We conclude that further investigation of the role of SGLT2 inhibition as a therapeutic strategy for patients with type 2 diabetes and pulmonary diseases causing CO_2 retention is required.

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References

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