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Effects of Dapagliflozin on Endothelial Function, Renal Injury Markers, and Glycemic Control in Drug-Naïve Patients with Type 2 Diabetes Mellitus (*Diabetes Metab J* 2019:43:711-7)

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We have read with great interest the elegant paper by Kong et al. [1], demonstrating that administration of dapagliflozin in drug-naïve patients with type 2 diabetes mellitus (T2DM) did not affect significantly systemic endothelial function, as measured by the reactive hyperemic index (RHI); however, it produced a significant decrease in body weight and homeostatic model assessment of insulin resistance (HOMA-IR) and promoted enhanced ketogenesis.

The interconnection between T2DM and endothelial dysfunction has been established a long time ago, with the latter representing an initial step towards the development and progression of cardiovascular disease [2]. Recent data suggest that patients with T2DM feature an impaired endothelial function, even in the context of well-controlled cardio-metabolic risk factors and low sodium intake, compared to normal and impaired glucose tolerance subjects [3].

Endothelial dysfunction plays an important role in the prediction of incident cardiovascular disease among patients with T2DM, while insulin resistance seems to augment this association; as shown formerly in the Hoorn study, patients with T2DM being at the highest tertile of HOMA-IR exhibit a 92% increase in the risk of incident cardiovascular events (hazard ratio, 1.92; 95% confidence interval, 1.42 to 2.60) per 1 standard deviation lower flow-mediated dilation (FMD), compared to those patients being at the lower HOMA-IR tertiles [4]. Thus, endothelial dysfunction appears to act synergistically with insulin resistance for the development of cardiovascular disease among patients with T2DM. It is therefore deduced that it should constitute a primary therapeutic target.

Recently, sodium-glucose co-transporter-2 (SGLT-2) inhibitors have attracted a significant amount of scientific interest due to their multiple pleiotropic, beneficial effects beyond glycemic control, mainly in terms of cardio- and reno-protection. Unfortunately, Kong et al. [1] failed to demonstrate a significant effect of dapagliflozin on endothelial function. On the contrary, Sugiyama et al. [5] have previously shown that the administration of dapagliflozin in uncontrolled T2DM patients for six months led to a significant improvement in endothelial function, as assessed by the natural logarithmic transformation of RHI (absolute change: 0.212 ± 0.252, $P<0.01$). Univariate and multivariate logistic regression analyses confirmed that dapagliflozin treatment was the only independent variable that predicted significantly the improvement in endothelial function [5]. Interestingly, in the DEFENCE study, which evaluated the effects of dapagliflozin on vascular endothelial function and glycemic control in patients with T2DM, Shigiyama et al. [6] showed that dapagliflozin administration for 16 weeks in patients with well-controlled T2DM on average

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and without macrovascular complications led to a non-significant increase in FMD; however, when the analysis was restricted to those patients featuring HbA1c levels greater than 7% at baseline, dapagliflozin was shown to produce a significant increase in FMD levels, compared to the metformin arm (P= 0.041). Based on their results, the researchers hypothesized that dapagliflozin might improve endothelial function by reducing oxidative stress [6]. A significant decrease in HOMA-IR with dapagliflozin was also confirmed [6]. Although both studies had a greater treatment duration than that performed by Kong et al. [1], Solini et al. [7] have previously demonstrated an acute treatment effect of dapagliflozin in patients with T2DM, showing a significant increase in FMD with dapagliflozin after 2 days of treatment, along with a significant decrease in pulse wave velocity. Again, the researchers observed a significant reduction in 24-hour urine isoprostanes levels, another marker of oxidative stress, with dapagliflozin administration, questioning the underlying mechanism by which dapagliflozin improves endothelial function [7]. Short-term dapagliflozin treatment has also been shown to improve microvascular function, as assessed by retinal capillary flow, in patients with T2DM [8].

Overall, it seems that dapagliflozin exerts significant effects on endothelial function in patients with T2DM, as it improves endothelial dysfunction indices, namely RHI and FMD. Those effects might implicate improvements in glycemic control, insulin resistance and decrease in oxidative stress; however, direct causality cannot be proven based on the available evidence. On the other hand, endothelial dysfunction is one of the major determinants of early vascular ageing and subsequently increased aortic stiffness. The latter has been established as an undoubted prognostic marker of cardiovascular disease incidence among patients with T2DM [9]. However, there is no crude evidence so far concerning the impact of dapagliflozin on aortic stiffness indices, as estimated by the corresponding "gold-standard" measure, namely pulse wave velocity.

Since dapagliflozin has been recently shown to decrease cardiovascular death and hospitalization for heart failure in patients with T2DM with established or at high risk of atherosclerotic cardiovascular disease [10], it is of outmost importance to determine whether its effects on endothelial dysfunction correlate with those beneficial cardiovascular effects. Further, relevant, prospective trials will shed light on this hypothesis. Finally, it has also to be determined whether the rest commercially available SGLT-2 inhibitors exert similar effects, establishing or not a class effect.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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