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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 appreciate Dr. Dimitrios' interest and insightful comments on our article entitled "Effects of dapagliflozin on endothelial function, renal injury markers, and glycemic control in drug-naïve patients with type 2 diabetes mellitus," which was published in *Diabetes and Metabolism Journal* [1]. In this research, we observed that dapagliflozin treatment did not change systemic endothelial function evaluated via reactive hyperemic index (RHI) and renal injury markers, except urine N-acetyl-beta-D-glucosaminidase in type 2 diabetes mellitus (T2DM). Dapagliflozin treatment improved insulin resistance, reduced body weight, and showed similar glycemic control to metformin in our study.

Endothelial dysfunction is considered as an early marker for atherosclerosis and involved in early atherosclerotic plaque formation, since the endothelium plays a major role in regulating vascular homeostasis via vasodilation, smooth muscle cell proliferation and migration, thrombogenesis, and fibrinolysis [2,3]. On the other hand, there is limited data about changes in endothelial function after sodium-glucose cotransporter-2 inhibitor treatment in human.

Unlike our study, the study by Sugiyama et al. [4] reported that add-on dapagliflozin therapy for 6 months improved endothelial function measured by RHI method in uncontrolled T2DM patients [4]. However, this study is different from ours in several aspects. First, the number of the participants was greater than ours (27 vs. 22 per group), but the difference does not seem significant because our study was a cross-over design. Second, Sugiyama's study was non-randomized, and the patients in the control group were taking heterogeneous medications for diabetes. On the other hand, the patients in our study were randomized and control patients took metformin. Third, the changes in glycosylated hemoglobin (HbA1c) levels were much higher than our study (1.2% vs. 0.5%). Fourth, absolute changes in RHI were higher than ours (0.212 vs. 0.130) although baseline RHI was similar.

In DEFENCE study, the researchers evaluated endothelial function using the flow-mediated dilation (FMD) method between metformin group and metformin with dapagliflozin group. As with our findings, they did not observe any significant difference between the two groups [5]. However, in a subgroup analysis of patients with HbA1c levels >7.0%, FMD was improved in the dapagliflozin add-on group. The study also has some different characteristics compared to our study; it was a parallel design, 16-week study, which was longer than our study, and enrolled more participants (40 vs. 22 per group) [5]. Although they did not report the change of HbA1c levels in the participants with HbA1c levels >7.0%, the changes in HbA1c levels in our study may be insignificant to affect endo-

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thelial function.

In our study, the changes in endothelial function could be less prominent because the participants were drug-naïve and had relatively low HbA1c levels. Limited sample size also may lead to underestimating treatment-related changes in endothelial function. Nevertheless, there is still a possibility that dapagliflozin treatment may not have a significant effect on endothelial function in participants with well-controlled T2DM.

To summarize, 8-week dapagliflozin treatment did not improve endothelial function in our study. Considering the previous studies and our result, the insignificant changes might be due to characteristics or a small number of participants, but there is also the possibility that the dapagliflozin treatment may not improve endothelial function in well-controlled T2DM patients.

CONFLICTS OF INTEREST

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

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