LETTER TO THE EDITOR

Reply to 'Effects of sodium-glucose cotransporter 2 inhibitors on urinary excretion of intact and total angiotensinogen in patients with type 2 diabetes' by Yoshimoto *et al.*

To the editors,

In the study published in this journal by Yoshimoto *et al*,[1] the authors show, for the first time in patients with Diabetes Mellitus (DM) type 2, the effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors (iSGLT2) on the urinary excretion of angiotensinogen. As the urinary angiotensinogen is directly correlated with the renin–angiotensin system (RAS)[2] activity into the kidney, the authors conclude that the iSGLT2 does not activate this system because there are no changes in the urinary angiotensinogen after the treatment.

We agree with the authors that the results should not be generalized and should be confirmed with additional studies because of the following four reasons.

First, the Yoshimoto *et al*[1] study has been performed using different iSGLT2, even though they work in a similar way, they do not have the same potency blocking the SGLT2 receptors. In addition, the doses used are not comparable. For example, 100 mg of canagliflozin would be equivalent to 10 mg of dapagliflozin instead of 5 mg, and the study did not consider this important difference.[3 4]

Second, of the 15 patients selected for the study, only nine completed the 4 weeks treatment which could justify that the results were not statistically significant and therefore a biggest sample may be needed to get consistent conclusions.

The third of our reasons regards the previous studies published. In humans, there are only two studies where RAS activation has been increased in patients with diabetes who received iSGLT2 therapy. One of them was performed in patients with type 1 DM using empagliflozin,[5] while the other was performed in patients with type 2 DM using dapagliflozin.[6] In both studies, plasma levels of angiotensin II (Ang II) and aldosterone (Ald) were increased instead of suppressed. We are going to focus on this study results in the next paragraphs.

Cherney *et al*[5] demonstrated the hemodynamic effects (measuring levels of Ang II and plasma Ald) caused by the treatment with empagliflozine at the renal level in a cohort of patients with type 1 DM with and without renal hyperfiltration. We would like to emphasize that it was exclusion criteria patients treated with diuretics or any drug acting on the RAS system. After treatment with empagliflozine for 8 weeks, patients with hyperfiltration showed a significant increase in Ang II and Ald values. The scientific rigor of the trial was confirmed through euglycemic and hyperglycemic clamp. In additional post hoc analysis of this study, intrarenal RAS activity was measured through urine determination of angiotensinogen, ACE, and ACE type 2.[7] All of these markers increased after treatment with empagliflozine indicating there was an activation of the intrarenal RAS.

The author's explanation of the increase in RAS activity, both systemic and renal, is modest and would respond to circulating volume depletion in a similar way to thiazide diuretics. This RAS activation would be insufficient to counteract the effect of volume depletion. In addition, an increase of hematocrit was observed which supports the existence of volume depletion as the cause of such activation.

The second study in humans was performed with dapagliflozin. Sixty-six per cent of the patients took drugs wich inhibited RAS, so the conclusions should not be generalized. In addition, to observe the effect on RAS was not the aim of the study.[6] The effects at RAS level are related to the circulating volume decrease that implies an increase of hematocrit.[6] In Yoshimoto *et al*'s[1] study, there is no increase of hematocrit, instead a decrease is shown (41%±6 before treatment an 38%±15 after treatment, p=0.54). Therefore, the conclusions do not support the existence of dehydration or volume depletion.

Finally, treatment with drugs which affect RAS can modify Ang II or Ald levels. ACE inhibitors decrease both plasma and intrarenal levels of Ang II. However, treatment with inhibitors of the Ang II AT1 receptor would allow Ang II to increase in plasma level by activating renin secretion by the juxtaglomerular cells, as well as the local generation of Ang II.[8 9] Yoshimoto *et al*[1] study did not specify what antihypertensive drugs were used; therefore, results should be interpreted with caution.

The iSGLT2 has many effects on the cardiovascular system. The mechanisms underlying these effects are not entirely known. In the review, we propose that it is clear iSGLT2 can modify the Ang II or Ald levels. It will be necessary to produce more studies, in which all the factors that affect the RAS system, such as antihypertensive medication, are considered.

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