Title

Biologically plausible trends suggesting that a low-protein diet may enhance the effect of flozination caused by the sodium-glucose cotransporter-2 inhibitor dapagliflozin on albuminuria

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LETTER TO THE EDITOR

Biologically plausible trends suggesting that a low-protein diet may enhance the effect of flozination caused by the sodium-glucose cotransporter-2 inhibitor dapagliflozin on albuminuria

We read the paper by van der Aart-van der Beek et al[1] with great interest and understand that a core message of this secondary analysis of three relatively small-sized randomized controlled trials is that high dietary protein intake does not offset the benefits of sodium-glucose cotransporter-2 (SGLT2) inhibition, also known as "flozination". However, it may also be true that low protein intake could offer additional synergistic benefits to patients undergoing flozination. We feel that the presented data could have been interpreted differently given that there appear to be clinically relevant and *biologically plausible* trends in support of combining a low-protein diet with SGLT2 inhibition to improve the salutary effects of this pharmacotherapy approach to reducing albuminuria and protecting kidney health and longevity.

In the DELIGHT trial (n = 233), dapagliflozin versus placebo reduced urinary albumin to creatinine ratio (UACR) by 21% in the high-protein-diet group versus 28% in the low-protein-diet group, suggesting 39% more effect of the SGLT2 inhibitor if combined with low protein intake. The interaction *P* value was not significant, probably because of the limited sample size. Interestingly, the IMPROVE trial (n = 30) showed a very similar trend in that there was 38% more effect of restricted protein intake added to the effect of dapagliflozin as compared to the pharmacotherapy alone or in combination with high dietary protein intake (Figure 1), although the *P* value for interaction was not significant. The third study, the DIAMOND trial (n = 53), significant showed a marginal effect of SGLT2 inhibition on UACR (*P* = 0.072). Dichotomization of dietary protein intake decreases statistical power. Treating dietary protein intake as a continuous variable could be more useful in this context, as methodologically implemented in other studies.[2]

We feel that these consistent trends from two separate trials of dapagliflozin, even though statistically nonsignificant, are consistent with the well-established data in the past, showing that a low-protein diet enhanced the effect of angiotensin-converting-enzyme inhibition or angiotensin receptor blockade on renal protection.[3,4] Indeed, a low-protein diet leads to contraction of the afferent arteriole of the glomeruli, resulting in reduced intraglomerular pressure, hence, opposing the renal hyperfiltration that is invariably harmful to kidneys in the long term[5]; this mechanism is similar to what flozination with such SGLT2 inhibitors as dapagliflozin appears to engender, given the modulation of the tubuloglomerular feedback that abrogates intraglomerular

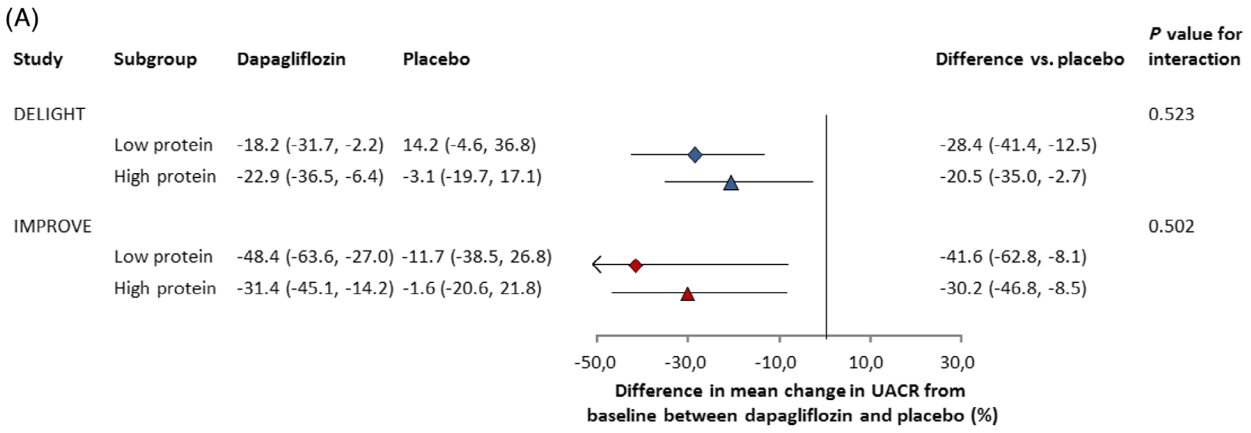

FIGURE 1 Biologically plausible trends suggesting that a low-protein diet enhances the effect of sodium-glucose cotransporter-2 inhibition on albuminuria (interaction *P* values are nonsignificant).[1] Adaption of panel A, from the figure in the study by van der Aart-van der Beek et al[1] highlighting the effect of dapagliflozin on urinary albumin-to-creatinine ratio (UACR) according to baseline dietary protein intake (from baseline to week 24 in the DELIGHT trial, and from baseline to week 6 in IMPROVE trial. DIAMOND study not shown here given nonsignificant UACR data)

pressure under SGLT2 inhibition.[6] High dietary protein intake, on the contrary, can aggravate glomerular hyperfiltration and weaken the salutary effect of SGLT2 inhibition on renal haemodynamics.[7]

The additional observation that dapagliflozin exhibited more estimated glomerular filtration rate preservation benefit in patients whose dietary protein intake was classified as high, suggests that high protein intake can cause an even larger effect size, probably by worsening glomerular hyperinflation,[8] so that the effect of SGLT2 inhibitors becomes more evident, whereas low-protein diets may dilute this effect in patients with chronic kidney disease given mitigation of hyperfiltration by lower dietary protein intake.[5] However, it is important to note that diet can be wrong in many ways other than its high protein or high meat content, including having excessive calories, inadequate fibre intake or high added preservatives. These and other important nutritional questions can be examined in future studies involving SGLT2 inhibitors in kidney disease with more formal assessments of dietary protein intake on a background of such medications as renin-angiotensin-aldosterone system inhibition and SGLT2 inhibition. What remains even less known is whether plant-based or plant-dominant low-protein diets, including the DASH and PLADO diets, would have an even stronger additive effect on renal outcomes under the SGLT2 inhibitory effects of dapagliflozin.[9,10] Given the important data and trends presented in their article,[1] an alternative title for the study by van der Aart-van der Beek et al[1] could have been: "Biologically plausible trends suggesting that a low-protein diet may enhance the effect of flozination on albuminuria". We advocate well-designed, randomized controlled trials examining the potentially synergistic effect of low-protein and plant-dominant diets on improving renal outcomes including under SGLT2 inhibition therapy.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

This is a letter to editors

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