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Improving Management of Diabetic Kidney Disease-will GLP-1 Receptor Agonists have a role?

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Improving Management of Diabetic Kidney Disease-will GLP-1 Receptor Agonists have a role?

Renal disease will affect around 40% of people with type 2 diabetes (T2D) and is a leading cause of morbidity and mortality(1).Management of Diabetic Kidney Disease (DKD) has traditionally focused on tight glycaemic (in the early stages) and blood pressure control the latter including agents which inhibit the renin-angiotensin system(1).Despite this, most patients with DKD experience a gradual decline in renal function eventually progressing to end stage renal disease and an increased risk of cardiovascular events and mortality. Glucagon like peptide-1 receptor agonists (GLP1-RAs) are established treatments for T2D which, in addition to glucose lowering, are associated with weight loss, blood pressure lowering and cardio-protection (2). There is a lack of clarity, however, on the long-term benefits of GLP-1RA therapy in DKD particularly in relation to glomerular function.

In their paper published in the Lancet D and E, Mann et al (3), report a post-hoc analysis of changes over a period of 30 weeks in glomerular function, albuminuria and safety from pooled data from SUSTAIN (1-5 and 7) studies and then separately from the longer term Cardiovascular Outcome Trial-SUSTAIN 6 (4). The GLP-1 RA, semaglutide, was associated with : (a) a fall in eGFR of 2.5 to 3.5ml/min during the first 12 weeks followed by stabilisation between 12-30 weeks in those with baseline eGFR >60ml/min, but less marked in those with significant renal impairment (b) a consistent and significant decrease in albuminuria more pronounced in those with established albuminuria (c) no excess risk of major renal adverse events including acute renal injury or urinary disorders.

Currently, most evidence for renal protection with GLP1-RAs comes from cardiovascular outcome trials (CVOTs)(5-7). Pre-specified sub-group analysis of data from these studies have shown an overall reduction in composite renal outcomes (incidence and progression of albuminuria, doubling of serum creatinine, requirement for renal replacement therapy and renal death). The reported benefits were mainly driven by a gradual reduction in albuminuria with only a minimal effect on glomerular function. The more acute fall in eGFR followed by evidence of stabilisation reported by Mann et al and seen in each of the individual SUSTAIN trials is surprising and not previously noted with GLP1-RA therapy.

Haemodynamic alterations following treatment with renin angiotensin and SGLT2 inhibitors are well recognized(8) .The resulting decrease in glomerular pressure has been associated

with prevention and/or reduction of albuminuria and delay in progression of DKD. This is therefore an area of significant interest in relation to GLP-1 RA therapy where the LEADER trial (6)and the exploratory analysis of the REWIND study(5) have previously reported significant reductions in albuminuria independent of glycaemic and blood pressure control with liraglutide and dulaglutide respectively. The findings of the present study suggest a similar reduction in albuminuria with semaglutide. Given that increasing levels of albuminuria are poor prognostic markers in DKD, such reductions in albuminuria with GLP-1 RAs are of interest, but emphasise the need for more studies to determine whether this is reflected in renal protection long term.

Whilst the inclusion of a large number of subjects and the consistency of the findings can be seen as a strength, a major limitation of this post-hoc analysis is that it is based on data pooled from different studies. This imposes restrictions on analysis and interpretation of the findings. For example, there is a significant degree of heterogeneity between the cohorts plus varying durations of follow up. Moreover, limiting duration of follow up to only 30 weeks is insufficient to provide information on the effects of semaglutide on progression of DKD and indeed on long term safety. It could be argued, however, that given the patient cohorts include those with large ranges of eGFR and albuminuria, this allows for a better understanding of the effects of semaglutide at different stages and severity of DKD. In addition, the findings that semaglutide was not associated with an increase in renal adverse events and particularly acute kidney injury or urinary disorders provide reassurance regarding its use for its primary indications.

Whilst these findings may be seen as highly relevant in the context of management of T2D and specifically in prevention and progression of associated DKD, significant questions remain. Reductions in albuminuria and hemodynamic changes affecting glomerular function are recognised markers indicating reno-protection, but DKD progresses over many years and there is little evidence whether these improvements will translate into reduction of progression to ESRD. Hopefully this critical point will be answered by the ongoing renal outcome studies such as Semaglutide Renal Outcomes Trial (FLOW).

Another question relates to establishing the role and positioning of GLP1-RA treatment in the management of DKD. For example, an agent from a different class of anti-diabetes therapies, the SGLT-2 inhibitor canagliflozin, effectively improves all renal outcomes (9) and studies

involving others in the class indicating similar benefits (10). To more clearly define the place of these agents in management, an understanding of the exact mechanisms through which SGLT2i and GLP1-RA exert their renal effects needs to be elucidated. If the mechanisms are different, could they have a complimentary role? Finally, despite the limitations of this type of analysis, these findings offer some reassurance and confidence in the use of GLP1-RA in patients with, or at risk of, DKD.

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