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Commentary

Non-albuminuric chronic kidney disease in diabetes: A different approach?

During the last five decades, elevated albuminuria has been used as the biomarker of choice to identify individuals with diabetes at risk for progression to kidney failure and cardiovascular disease[1,2]. Since 2001, standard treatment of Type 2 diabetes (T2D) and nephropathy has been the use of renin-angiotensin system blockade after landmark studies which employed losartan and irbesartan[3-5].

After two decades of little progress in the treatment of diabetic kidney disease, which included the fall of dual renin-angiotensin system blockade[6,7], we are now experiencing a great leap forward, following the guideline for the induction of sodium-glucose co-transporter 2 inhibitors (SGLT2i)[8,9] and the novel non-steroidal mineralocorticoid receptor antagonist, finerenone[10,11]. Concurrently, there is an increased interest in the group of individuals with T2D with chronic kidney disease (CKD) that does not display elevated albuminuria levels. Amongst many other cohort studies, the Italian RIACE study[12] documented the prevalence and prognosis of the non-albuminuric CKD in diabetes, however only a few dedicated intervention studies have been performed so far. In the tertiary diabetes speciality clinic at the Indian Institute of Diabetes, Thiruvananthapuram, Jayakumari *et al*[13] performed a retrospective study to examine the prevalence of CKD and characteristics of their diabetes population.

By extracting data from the medical records, the authors found that amongst a total of 3534 T2D individuals, 2379 (67.3%) did not have CKD, 956 (27.2%) had elevated albuminuria only, 121 (3.4%) had CKD and high albuminuria and 75 (2.1%) had CKD only. It was clear from the data that the proportion of non-albuminuric CKD was highest in CKD stage 3A (45%) and lowest in CKD stage 4 and 5 (10%). In this cohort, non-albuminuric CKD then made up about one-third of individuals with CKD, leaving the clinician with important questions regarding aetiology, prognosis and treatment. While duration of diabetes was similar between the albuminuric and the non-albuminuric CKD groups, the latter was markedly older, and had less cases with retinopathy, indicating that aetiology may in fact be something other than microvascular changes. Long-standing hypertension, perhaps undetected, can be a frequent cause. As often is the case, only a kidney biopsy would be able to shed further light on the causes of the condition. How about prognosis? As the authors demonstrate and discuss referring to findings from other studies, it seems that non-albuminuric CKD in T2D carries similar cardiovascular risk as the albuminuric CKD, while the risk for kidney failure is lower. This should be comforting news for the patient and a focus could shift more onto cardiovascular prevention. Of note, 50.6 per cent of the non-albuminuric CKD group were on statin therapy, a proportion that perhaps could be increased with this in mind. How about therapy for this group? In any case, renin–angiotensin system blockade will still be a standard therapy for this group, and in the study, 45.3 per cent of the patients received angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. A case can be made for the addition of SGLT2i treatment, as a risk-reducing potential across a number of studies and diabetes phenotypes has been shown and previously guidelines are recommended[14]. Equal in terms of a priority for guideline recommendation for this population is using a glucagon-like peptide-1 receptor agonist with a proven cardiovascular benefit. This leaves the treating clinician with some options in terms of treatment of the discussed patient phenotype, with a special focus on cardiovascular protection. But what about progression of CKD? The EMPA-KIDNEY study[15] with the SGLT2i, empagliflozin, may provide the answer, as a significant proportion of the included population have diabetes with non-albuminuric CKD. The study was, however, stopped early due to the overwhelming

efficacy. The overall results in the non-albuminuric CKD group (one third T2D) reportedly indicated a lack of efficacy regarding the primary outcome (progression of CKD or death from cardiovascular cause), perhaps due to a lower overall risk of CKD progression in that group. However, there was a significant improvement in the long-term eGFR slope in the intervention group.

In conclusion, it is fair to say that persons with normoalbuminuric CKD in T2D carry elevated risk, and interventions decrease that risk, but it may not be in the same order of magnitude as in individuals with albuminuria.

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