



EDITORIAL COMMENT

Diabetes mellitus: a single cardiorenal syndrome umbrella

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Diabetes and chronic kidney disease are among the fastest-growing causes of death worldwide. An optimized conceptual framework on the pathogenesis of diabetic kidney disease and its interplay with cardiovascular disease will facilitate the development of monitoring and therapeutic strategies to decrease the risk for severe clinical events and early mortality. In this issue of *ckj*, Pinier *et al.* provide data supporting the existence in diabetic patients of a single cardiorenal syndrome umbrella, rather than separate cardiorenal or renocardiac entities (e.g. acute cardiorenal syndrome or chronic renocardiac syndromes).

Keywords: acute tubular necrosis, AKI, cardiorenal syndrome, chronic renal failure, chronic renal insufficiency

Diabetes and chronic kidney disease (CKD) are among the fastest-growing causes of death worldwide [1, 2]. An optimized conceptual framework on the pathogenesis of diabetic kidney disease and its interplay with cardiovascular disease will facilitate the development of monitoring and therapeutic strategies to decrease the risk for severe clinical events and early mortality. The French Clinical Research Infrastructure Network Investigation Network Initiative-Cardiovascular and Renal Clinical Trialists (F-CRIN INI-CRCT) is providing a steady stream of new information on this topic. One of its endeavours is a well-characterized retrospective cohort of 861 outpatients with type 2 diabetes followed up in a single centre by nephrologists [3]. In this issue of *ckj*, Pinier *et al.* assess the impact of prevalent and incident cardiovascular events on the risk for end-stage renal disease (ESRD) and acute kidney injury (AKI) in this cohort [3]. Both baseline and incident major cardiovascular events (atrial fibrillation, heart failure, acute coronary syndrome) were shown to be powerful risk factors for AKI and ESRD, although

the association between acute coronary syndrome and ESRD was no longer significant after multivariate adjustment. Since a reduced estimated glomerular filtration rate was associated with an increased risk for major cardiovascular events, the authors proposed that these results support the concept of a 'single cardiorenal syndrome umbrella', i.e. acute and chronic cardiovascular events increase the risk for AKI and ESRD, and conversely acute and chronic renal events increase the risk for new cardiovascular events, at least in patients with diabetes mellitus.

Type 2 diabetes mellitus is highly prevalent and a powerful and classical risk factor for CKD and AKI, and thus provides the basis for a good model to study the interplay between cardiovascular and renal diseases. AKI episodes are associated with a higher risk for the development of CKD, cardiovascular events and overall mortality [4–10]. Additional risk factors for progression to CKD include diabetes mellitus, hypertension, heart failure, and both baseline renal function prior to the onset of AKI

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and the severity of AKI episodes [7, 8]. In diabetic patients, repeated episodes of AKI may occur in up to one-third of patients who survive initial hospitalization for AKI, and each AKI episode is associated with a cumulative increase in the risk for reaching CKD stage 4 [5]. The mechanisms underlying the association between AKI episodes and the higher risk for developing CKD, cardiovascular events and overall mortality remain poorly understood [11]. A lack of recovery of measurable and unmeasurable parameters of renal function following an AKI episode is thought to be an important contributor to the prevalence and development of CKD [12]. Loss of certain features of renal function not routinely assessed in clinic, such as the expression of Klotho, a reno- and cardio-protective factor, may not recover despite improvement in the glomerular filtration rate [13]. In this regard, even AKI patients with fully recovered renal function still remain at risk for long-term renal complications [11, 12, 14]. Thus, it remains uncertain to what extent the association between AKI and adverse outcomes is due to AKI itself or is as a result of the development of CKD [15]. Our group has determined the outcomes of 219 patients with complete recovery of renal function following mild AKI [14]. The rates of cardiovascular events and associated mortality were higher in patients with type 2 diabetes, those with hypertension and those who developed CKD. Up to 18% of patients developed CKD after 4 years, but interestingly, AKI episodes were found to have a short-term (1 year), but not long-term (4 years), impact on CKD development and mortality, highlighting the relevance of classical risk factors such as diabetes mellitus.

Recurrent AKI episodes have a strong impact on kidney outcomes and patient survival [14]. AKI recurs in about one-third of patients who survive an initial AKI episode, most commonly in the first year following hospitalization, with 44% of AKI episodes occurring within 6 months of the first AKI episode. Such early recurrence could be explained by subclinical residual damage, which may itself increase the vulnerability to subsequent kidney insults [16, 17]. Recurrent AKI causes a 2.2-fold increase in the risk for CKD, a 31-fold increase in the risk for major cardiovascular events and a 4.5-fold increase in mortality risk within 4 years of first AKI episode [14]. Optimizing management following AKI remains problematic, and the transition of care from hospitalization to nephrologist may be an opportunity to implement strategies for the prevention of long-term loss of renal function and its consequences [18]. In this regard, few AKI survivors are referred for nephrology follow-up [19].

Pinier et al. emphasized a dynamic relationship between AKI and CKD and acute and chronic cardiovascular events, as well as mortality, in type 2 diabetes patients. Of note, published data suggest that this relationship may be applicable also to different populations. Unfortunately, the increased occurrence of AKI and ESRD was observed despite follow-up by a nephrologist. This illustrates deficiencies in our current monitoring and therapeutic approach to diabetic kidney disease. The concept of a single cardiorenal syndrome umbrella may help guide research and clinical care, emphasizing a multidisciplinary approach and the development and implementation of adequate preventive surveillance strategies.

CONFLICT OF INTEREST STATEMENT

None declared.

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