Defining Improvement in Chronic Kidney Disease: Regression and Remission

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Abstract

Purpose of Review: International definitions exist for chronic kidney disease (CKD) progression and kidney failure but despite evidence that kidney function may improve, there are no agreed definitions for regression and remission of CKD. In the light of recent novel kidney protective therapies and the promise of regenerative medicine to reverse kidney damage, it is time to critically examine these neglected aspects of CKD epidemiology.

Recent Findings: We propose that CKD regression is viewed as a process of improvement defined as a sustained increase in GFR by ≥25% and an improvement in GFR category or increase in GFR of 1≥ml/min/year, whereas remission is considered a category of improvement defined as GFR ≥60 ml/min/1.73m^2 and UACR <30 mg/g. Several recent studies have reported improvement in kidney function in populations with CKD, even in the absence of specific therapy. Regression and remission of CKD are associated with increased likelihood of sustained improvement in kidney function as well as improved survival.

Summary: Further research is warranted to validate the proposed definitions and investigate associated mechanisms. We look to a future in which the goal of therapy is not merely to slow CKD progression but to improve kidney function and seek a cure.

Keywords: 3-5 keywords relevant to the paper should be listed. chronic kidney disease, outcomes, progression, regression, remission

Introduction

Chronic Kidney Disease (CKD) is defined in the Kidney Disease Improving Global Outcomes (KDIGO) guideline as "abnormalities of kidney structure or function,

present for at least three months, with implications for health" [1]. Despite some controversy related to the applicability of this definition to older people [2], the global acceptance of a single definition has facilitated important studies that have greatly improved understanding of the epidemiology of CKD. Understandably, the focus has been on studying adverse outcomes associated with CKD and in the process, international definitions have been proposed for CKD progression (decrease in GFR by ≥25% and deterioration in GFR category) [1] and kidney failure (kidney transplant, maintenance dialysis, and death from kidney failure or GFR decline to <15 ml/min/1.73m^2 or ≥40% decline in GFR) [3]. Epidemiological studies have identified that the risk of adverse outcomes associated with CKD is variable and can be predicted by simple clinical risk factors. To facilitate personalised medicine, considerable progress has been made in developing risk prediction tools to identify those at greatest risk [4].

Nevertheless, this welcome progress has largely neglected the fact that a large proportion of those with CKD (the majority in some populations) are at low risk of adverse outcomes and that CKD does not progress in all persons who meet the definition. Importantly, kidney function may improve in some persons, either spontaneously or in response to therapy. The terms "remission" and "regression" are used to describe improvements in kidney function, most commonly in the context of response to therapy for immune-mediated kidney diseases, but there are no internationally agreed definitions for these terms in relation to CKD, and consequently it has been difficult to study these aspects in a standardised manner across different populations. Ironically, we are currently unable to define the very outcomes we (and our patients) most desire. Furthermore, though there is an

international definition for CKD, there is no agreed definition for when CKD is no longer present or "cured", implying that once diagnosed, CKD is permanent. Thus, even if kidney function improves permanently, persons continue to be labelled as having CKD with potential negative implications for their employment prospects, insurance costs and mental wellbeing.

The recent publication of several trials of novel kidney protective therapies has ushered in an era of substantially more effective therapeutic approaches that will likely result in more patients evidencing improved kidney function. Moreover, regenerative medicine approaches promise to provide novel techniques for repairing kidney damage to restore kidney function. It is therefore time to critically examine these neglected aspects of CKD epidemiology. In this brief review we will propose definitions for "regression" and "remission" and consider published data on improvement in kidney function within the context of CKD to prompt discussion and facilitate future research on this important topic.

Terminology and Definitions

The terms "regression" and "remission" are widely used in medical literature including with reference to CKD but lack precision without a specific definition. In the Oxford English Dictionary (OED), regression is defined as "reversal or resolution of a physiological or pathological process" whereas remission is "lessening of the severity of a disease or symptom; disappearance of symptoms or cessation of the activity of a disease for a period" [5]. There is therefore considerable overlap in meaning and the words could be considered synonymous.

Regression

With reference to CKD, Cortinovis et al. proposed that regression should refer to a state of improvement in CKD defined by proteinuria <0.3 g/24 hours, increasing GFR and improving structural changes [6]. On the other hand, Liu et al. viewed CKD regression as "sustained kidney function improvement" (the opposite of CKD progression) defined as sustained, higher eGFR category for longer than 3 months and a 25% or greater increase in the eGFR from baseline [7]. An additional approach to defining regression is to consider change in GFR over time. In healthy persons GFR is stable over time or may decrease by a mean of 0.72 ml/min/1.73m^2/year in men and 0.92 ml/min/1.73m^2/year in women after age 50 years [8]. Thus, regression could also be defined as a sustained improvement in GFR of ≥1ml/min/year.

Remission

The term "remission" is frequently used in medicine to refer to a state of improvement in cancer. For example, the National Cancer Institute defines remission as "A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body" [9] . In nephrology literature, remission is frequently used to describe response to immunosuppressive medication, often in the context of nephrotic syndrome. In this scenario, complete remission usually refers to complete resolution of proteinuria whereas partial remission refers to a reduction in proteinuria. Cortinovis et al. proposed that remission should refer to a state of improvement in CKD defined by proteinuria <1 g/24 hours, stable GFR and stable structural changes [6]. On the other hand, Shardlow et al. considered remission as a state in which there is no evidence of CKD, defined by GFR >60 ml/min/1.73m^2 and UACR <3

mg/mmol in persons who previously met the diagnostic criteria for CKD [10]. This definition of remission was also adopted by Hirst et al [11].

Based on these considerations, we propose that regression should be viewed as a process of improvement (as suggested by the OED definition) whereas remission should be considered a category of improvement. Thus, regression is viewed as the opposite of progression as proposed by Liu et al [7]. On the other hand, remission is the category that is the opposite of "relapse". For CKD to be considered cured, a sustained period in remission in the absence of therapy is required. Further research is warranted to identify what duration of remission is required to define a cure, such that the risk of future CKD and associated adverse outcomes including cardiovascular events and premature death are no different to the general population. The relationship between these concepts and proposed definitions are summarised in Figure 1.

Regression and remission of CKD in clinical studies

CKD Regression

Ruggenenti and Remuzzi et al. proposed the concept of a "Remission Clinic" designed to facilitate optimisation of anti-proteinuric therapies to achieve maximal renal protection [12]. Among 56 consecutive participants with 3 g/24 hours proteinuria at baseline despite treatment with an angiotensin-converting enzyme inhibitor, regression (proteinuria <0.3 g/24 hours) or remission (proteinuria 0.3 to 1.0 g/24 hours) of CKD was achieved in 26 (46%) participants and during seven years of observation, only two progressed to end-stage kidney disease (ESKD) versus 17 of 56 matched controls. Moreover, the rate of GFR decline was significantly slower in participants who achieved a reduction in proteinuria to <1g /24 hours versus those

with persistent proteinuria [12]. In a multicentre study based in 47 nephrology centres in Italy, regression was defined as a positive value for change in GFR over time. Using this definition, regression was observed in 391 (27.6%) of 1418 participants during an observation period of 18-24 months (median 23 months). Regression was independently predicted by lower magnitude of proteinuria, lower systolic blood pressure, higher body mass index and absence of autosomal dominant polycystic disease. Furthermore, regression was associated with a significantly lower risk of developing ESKD (hazard ratio = 0.28; 95% CI 0.14–0.57). A limitation of this study was that change in GFR was calculated as the difference between single baseline and follow-up values and was therefore subject to the statistical phenomenon of regression to the mean. However, in a subgroup of 1154 participants with at least three GFR values available, regression based on a positive GFR slope was observed in 29.6% [13]. In a population-based cohort study in Canada, Liu et al. utilised linked administrative and laboratory data to study outcomes in participants with incident CKD (mild/KDIGO category G3a, n=81,320; moderate KDIGO G3b, n=35,929; severe/KDIGO G4, n=12,237) using definitions of progression and regression as described above. They observed that the 5-year incidence of CKD regression was similar to the probability of progression or ESKD in mild (14.3% vs. 14.6%), moderate (18.9% vs. 16.5%) and severe (19.3%vs 20.4%) CKD. Moreover, an increase in mortality rate with increasing age in those with moderate and severe CKD resulted in a reduction in the risk of progression/ESKD in older participants whereas the likelihood of regression was less affected. Thus, with advancing age, CKD regression and death were more likely than progression and ESKD. Participants with severe albuminuria were less likely to experience regression. Of those who evidenced regression from mild CKD, 67.4% still had and

estimated GFR of >60ml/min/1.73m^2 after 5 years and overall, those who evidenced

regression were more likely to remain in the improved CKD category or experience

further improvement than progression, regardless of age and CKD severity [7].

CKD Remission

CKD remission (defined as GFR >60 ml/min/1.73m2 and UACR <3 mg/mmol) has

been studied in two cohorts of participants enrolled from primary care in the UK and

followed prospectively. In the Renal Risk in Derby (RRID) study, 1741 participants

with CKD category G3 were enrolled. CKD was generally mild (mean eGFR at

baseline 53 ml/min/1.73m^2) and only a small proportion (16.9%) had albuminuria.

After five years of observation the most likely outcome was stable CKD (34.1%) and

remission was observed in 19.3%. Progression of CKD was observed in 17.7% and

only four participants (0.2%) developed ESKD. Remission observed at baseline and

sustained at 1 year was associated with a very high likelihood of remission at 5 years

(odds ratio (OR) = 23.6, 95% CI 16.5–33.9, relative to participants with no remission

at baseline and year 1 study visits) whereas remission at baseline only (OR = 5.9,

95%, CI 3.8–9.2) and year 1 only (OR = 7.1, 95% CI 4.3–11.8, p < 0.001) evidenced

an intermediate likelihood of remission at 5 years. Participants with remission at

baseline and year 1 also evidenced lower mortality over 5 years (3.2%) compared

with those with remission at baseline only (5.0%) and those with remission at year 1

only (5.3%) or no remission (15.7%). Importantly, remission was predicted by simple

baseline variables age, sex, GFR and UACR (area under receiver operating

characteristic curve = 0.85) [10]. In the Oxford Renal Cohort Study (OxRen), 666

participants aged ≥60 years with CKD category 1-4 were enrolled (baseline mean

estimated GFR 55.9 and 68.3 ml/min/1.73m^2 in previously and newly diagnosed

cases, respectively). Overall, 7% experienced CKD progression (KDIGO definition)

during a median observation period of 2.1 years and of 394 participants who met the diagnostic criteria for CKD at baseline, 82 (21%) evidenced remission at some point during follow-up [11]. Data from the RRID and OxRen studies also demonstrated that participants moved in both directions from CKD to remission or vice versa. In RRID study, 26-29% of participants were in remission at any one time point [10] and in the OxRen study, 27-37% of participants were in remission at any one time point [11]. Remission has also been used as an outcome in clinical trials. In a prospective randomised trial of gastric bypass versus best medical treatment in participants with early-stage CKD, type 2 diabetes and obesity, the primary outcome was remission of albuminuria (defined at UACR<30mg/g) at 24 months and a secondary outcome was remission of CKD (defined at UACR<30mg/g and GFR>60 ml/min/1.73m^2). Remission of albuminuria was observed in 82% of those who underwent gastric bypass versus 55% of those who received best medical treatment (p=0.006) and remission of CKD was observed in 82% versus 48% (p=0.002) [14].

Mechanisms of improvement in CKD

In concert with understanding the epidemiology of CKD improvement, it is important to understand the mechanisms that may contribute to the reversal of kidney damage (Table 1). As discussed above, several studies have reported "spontaneous" improvement in CKD which may reflect artefacts such as loss of muscle mass or change in diet that impact serum creatinine concentration, unreported factors such recovery of acute kidney injury or change in medication (e.g. cessation of diuretics or non-steroidal anti-inflammatory drugs), relief of urinary obstruction or true spontaneous reversal of kidney damage. Additionally, there is limited evidence that if causative factors are removed, kidney function may improve over time. For example,

in response to weight loss after bariatric surgery, proteinuria improved and GFR increased over 24 months [14]. Additionally, in persons with diabetic nephropathy and type 1 diabetes, pancreas transplantation that resulted in euglycemia was associated reversal of kidney damage as evidenced by a reduction in thickness of glomerular and tubular basement membrane thickness and mesangial fractional volume, albeit over a prolonged period of ten years [15]. In kidney disease associated with immune-mediated inflammation it is well-recognised that immunosuppression may be successful in reversing inflammation and kidney damage. Immunosuppression has been reported to reverse kidney damage in animal models of CKD [16] but this has not yet been demonstrated in non-immune mediated CKD. Anti-inflammatory and antifibrotic therapies also show promise in animal models but have not yet been shown to reverse kidney damage in clinical trials. Further research is warranted to better understand the mechanisms that contribute to the reversal of kidney damage to inform the development novel therapies to improve kidney function.

Conclusion and Recommendations

There is a growing body of published evidence that kidney function may improve in the context of CKD and with the development of novel therapies, this is likely to become an increasingly likely outcome. Moreover, limited evidence indicates that short term improvements are associated with a higher likelihood of sustained improvement and with better long-term outcomes, including survival. We suggest therefore that the focus of CKD research should be broadened to include both progression and regression. We have proposed definitions for "regression" and "remission" and recommend that these should be debated and considered by

international guideline groups like KDIGO with the goal of reaching consensus. This is essential to facilitate future research which should investigate kidney function improvement in diverse CKD populations, identify predictors of CKD improvement and explore the biological mechanisms that reverse kidney damage. Future clinical trials should report regression and remission as outcomes, in addition to progression. Indeed, we should look forward to a future in which the goal of therapy is not merely to slow the rate of CKD progression but to improve kidney function and to seek a cure.

Key Points

- Despite evidence that kidney function may improve, there are no agreed definitions for regression and remission of CKD.

- CKD regression is viewed as a process of improvement defined as a sustained increase in GFR by ≥25% and an improvement in GFR category or increase in GFR of 1≥ml/min/year.

- Remission is considered a category of improvement defined as GFR ≥60 ml/min/1.73m^2 and UACR <30 mg/g.

- Several recent studies have reported improvement in kidney function in populations with CKD, even in the absence of specific therapy.

- Further research is warranted to validate the proposed definitions and investigate associated mechanisms.

Conflict of interest: none

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Figure Legends

Figure 1. Concepts and proposed definitions for regression and remission of chronic kidney disease.

Abbreviations: CKD – chronic kidney disease; GFR – glomerular filtration rate; KDIGO – Kidney Disease Improving Global Outcome; UACR – urine albumin to creatinine ratio