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Progression and fibrosis

Acute kidney injury and chronic kidney disease: From the laboratory to the clinic☆

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ABSTRACT

Chronic kidney disease and acute kidney injury have traditionally been considered as separate entities with different etiologies. This view has changed in recent years, with chronic kidney disease recognized as a major risk factor for the development of new acute kidney injury, and acute kidney injury now accepted to lead to de novo or accelerated chronic and end stage kidney diseases. Patients with existing chronic kidney disease appear to be less able to mount a complete 'adaptive' repair after acute insults, and instead repair maladaptively, with accelerated fibrosis and rates of renal functional decline. This article reviews the epidemiological studies in man that have demonstrated the links between these two processes. We also examine clinical and experimental research in areas of importance to both acute and chronic disease: acute and chronic renal injury to the vasculature, the pericyte and leukocyte populations, the signaling pathways implicated in injury and repair, and the impact of cellular stress and increased levels of growth arrested and senescent cells. The importance and therapeutic potential raised by these processes for acute and chronic injury are discussed.

1. Introduction

Chronic kidney disease and acute kidney injury have been recognized as important but distinct pathologies since their original descriptions by physicians such as Bright, Heberden and Abercrombie in the 19th century [1–3]. Until recent years, convention held that oliguric acute kidney injury was often fatal if untreated, but with the advent of dialysis complete recovery was often possible [4,5]. Chronic kidney disease was considered a separate, irreversible and often progressive entity leading to end stage renal disease.

2. Linking the epidemiology of acute kidney injury and chronic kidney disease

In recent years, standardized criteria have been adopted to allow consistent assessment of degrees of acute kidney injury, and their impact on early mortality and subsequent renal function in survivors [6,7]. With improved sample size, assessment criteria and length of follow-up, there are now strong data in support of three findings that: (1) pre-existing chronic kidney disease is a major risk factor for the development of acute kidney injury [8–10]; (2) patients with chronic kidney disease who develop acute kidney injury often recover incompletely and experience worsened subsequent renal deterioration [8,11,12]; and (3) the survivors of de novo acute kidney injury are more likely to develop proteinuria, increased cardiovascular disease risk and progressive chronic kidney disease than matched control patients without acute kidney injury [8,12–14] (summarised in Table 1).

Hence, acute kidney injury and chronic kidney disease are interlinked, with complete recovery from acute kidney injury far less common than previously assumed, and pre-existing chronic kidney disease priming the kidney for subsequent injury and maladaptive repair. In this review, we will discuss functions of the kidney implicated in acute kidney injury and chronic kidney disease, and examine the clinical and experimental evidence for their role in determining levels of acute renal injury and adaptive compared to maladaptive renal repair.

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Table 1
Clinical studies of interactions between acute kidney injury and chronic kidney disease.

Study	Population sample/size	Risk of acute kidney injury	Effects of chronic kidney disease on acute kidney injury	Effects of acute kidney injury on chronic kidney disease or end stage renal disease	Comments
Ishani et al. 2009 [8]	$n = 233,803$ Inpatients aged >67 years. Medicare in year 2000	3.1% in survivors	12% of total patients had chronic kidney disease 34.3% of patients acute kidney injury had chronic kidney disease	5.3 per 1000 developed end stage renal disease. Twenty-five percent had prior acute kidney injury	Relative risk of end stage renal disease was 41.2 in patients with acute kidney injury and chronic kidney disease, 13.0 in patients with acute kidney injury only
Xue et al. 2006 [9]	$n = 5,403,015$ Medicare discharges 1992–2001	23.8 cases per 1000 discharges Age, male gender and black race associated with risk	No data	No data	Risk of death at 90d was 13.1% without acute kidney injury, 34.5% with acute kidney injury as the principal diagnosis, and 48.6% with acute kidney injury as a secondary diagnosis
Coca et al. 2012 [11]	13 studies, $>1,000,000$ participants	No data	No data	Acute kidney injury resulted in a pooled hazard ratio for new chronic kidney disease of 8.82 and of end stage renal disease of 3.1	Survivors of acute kidney injury had a pooled hazard ratio for death of 1.98
Wald et al. 2009 [12]	3769 patients with acute kidney injury 13,598 controls (1996–2006)	No data	No data	Rate of end stage renal disease in patients with acute kidney injury of 2.63 per 100 person years, vs 0.9 in controls	An episode of acute kidney injury resulted in a hazard ratio for end stage renal disease of 3.23
Chawla et al. 2011 [13]	$n = 5351$ patients with acute kidney injury	No data	No data	13.6% of survivors developed chronic kidney disease 4	Age of patient and severity of acute kidney injury both predicted subsequent chronic kidney disease
Chertow et al. 2005 [15]	$n = 19,982$ total patients 1997–1998	13.1% of inpatients had acute kidney injury (by AKIN1 criteria)	Pre-existing chronic kidney disease was a significant risk factor for acute kidney injury	No data	
Coca et al. 2007 [16]	8 studies in total $n = 78,855$				Creatinine increases of 10–24% increased RR of 30d mortality by 1.8 ×, rises of $>50\%$ increased relative risk by 6.9 ×
Liano et al. 2007 [5]	$n = 187$ patients with acute tubular necrosis. Mean follow-up of 7.2 years	All patients had biopsy proven acute tubular necrosis	No previous nephropathies were seen	11/57 patients followed up had mild/moderate chronic kidney disease	
Vikse et al. 2008 [14]	$n = 570,433$ females (1967–1991)	3.7% of pregnant ladies developed pre-eclampsia		1 x prior pre-eclampsia resulted in relative risk of end stage renal disease of 4.7. Two+ prior pre-eclampsias had a relative risk of end stage renal disease of 15.5	
James et al. 2015 [10]	8 control studies n = 1,285,045 and 5 chronic kidney disease studies n = 79,519	In control patients, 0.2–6% developed acute kidney injury vs 2–25% in chronic kidney disease studies	Lower eGFF and higher albumin: creatinine ratio conferred higher acute kidney injury risk	No data	
Heung et al. 2015 [17]	VA inpatients $n = 17,049$ with acute kidney injury, $n = 87,715$ without acute kidney injury		No patients had documented chronic kidney disease prior to the study	Rate of recovery of acute kidney injury equated to a 2-year relative risk of new chronic kidney disease 3+: <3 days relative risk 1.43 3–10 days relative risk 2.0 >10 days relative risk 2.65	

Several studies and meta-analyses have been performed in the last 10 years examining the impact of chronic kidney disease on rates of acute kidney injury in hospital inpatients, and the impact of de novo acute kidney injury on subsequent kidney function and rates of end stage renal disease in survivors.