Acute Kidney Injury: A Bona Fide Complication of Diabetes

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Diabetes 2020;69:2229–2237 | https://doi.org/10.2337/db20-0604

The landscape of kidney disease in diabetes has shifted. The classical dogma of "diabetic nephropathy" progressing through stages of albuminuria, leading to decline in glomerular filtration rate and end-stage kidney disease (ESKD), has been replaced by a more nuanced understanding of the complex and heterogeneous nature of kidney disease in diabetes. Paralleling this evolution, standardized definitions have resulted in a growing appreciation that acute kidney injury (AKI) is increasing in its incidence rapidly and that people with diabetes are much more likely to develop AKI than people without diabetes. Here, I propose that AKI should be considered a complication of diabetes alongside other complications that similarly do not fit neatly into the historical microvascular/macrovascular paradigm. In this article, we take a look at the evidence indicating that diabetes is a major risk factor for AKI and we review the causes of this increased risk. We consider the long-term implications of AKI in diabetes and its potential contribution to the future development of chronic kidney disease, ESKD, and mortality. Finally, we look toward the future at strategies to better identify people at risk for AKI and to develop new approaches to improve AKI outcomes. Recognizing AKI as a bona fide complication of diabetes should open up new avenues for investigation that may ultimately improve the outlook for people living with diabetes and at risk for kidney disease.

The outlook for a person diagnosed with diabetes today is quite different from the outlook for a person diagnosed with diabetes 60 years ago (1). Life expectancy has improved (1) but remains short of the life expectancy of a same-aged person without diabetes (2). Concurrently, the complications landscape has shifted too. The dichotomous classification of complications as being "microvascular" or "macrovascular" has been (or should be) assigned to the archives, and the importance of other complications of diabetes (e.g., heart failure, cancer, cognitive decline, fractures, and liver disease) has rightfully gained traction. For kidney disease, the historical paradigm of "diabetic nephropathy" has given way to a more nuanced understanding of the heterogeneous manner by which kidney dysfunction may manifest in diabetes. Here I make the case that, aligned with this evolving appreciation, it is now time to recognize that acute kidney injury (AKI) is a bona fide complication of diabetes.

Defining AKI

When Mogensen, Christensen, and Vittinghus (3) published their seminal description of the five stages of diabetic nephropathy in 1983, there was no contemporary classification system for AKI. Acute insults to the kidney were typically termed "acute renal failure" and categorized according to the clinical presumption of the site of injury: "prerenal," "renal," and "postrenal." The absence of a standardized classification system presented challenges in defining the epidemiology of AKI and the extent of its impact, and thus, over the ensuing decades, efforts were made to harmonize reporting. In 2004, the Acute Dialysis Quality Initiative presented the first consensus definition of acute renal failure, termed RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) (4). Then, 3 years later, the Acute Kidney Injury Network (AKIN) proposed use of the term "AKI" to represent the spectrum of acute renal failure, and it made modifications to the RIFLE classification (5). Most recently, in 2012, Kidney Disease: Improving Global Outcomes (KDIGO) published its Clinical Practice Guideline modifying the RIFLE and AKIN criteria to provide a single unifying definition and staging system for AKI (6) (Tables 1 and 2). With these improvements in AKI definition, a clearer picture has emerged as to precisely how common AKI actually is, particularly among persons with diabetes.

AKI Is a Growing and Costly Health Care Burden

Contemporary estimates are that AKI complicates ~10–15% of all hospitalizations (7). AKI is thought to

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Received 7 June 2020 and accepted 7 August 2020

Table 1—KDIGO definition of AKI

Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h, or
Increase in serum creatinine to ≥1.5 times baseline that is known or presumed to have occurred within the prior 7 days, or
Urine volume <0.5 mL/kg/h for 6 h

Adapted from KDIGO Clinical Practice Guideline for Acute Kidney Injury (6).

affect >13 million people each year, >80% of whom live in the developing world, and it contributes to ~1.7 million deaths annually (8,9). In 2014, it was estimated that in England alone the annual cost of AKI-related inpatient care was a little over £1 billion or 1% of the total budget of the National Health Service (10). The annual incidence of AKI is also rising at an alarming rate. For instance, administrative data from the Centers for Disease Control and Prevention indicate that the number of hospitalizations with AKI increased more than fourfold between 2000 and 2014, rising from 953,926 hospitalizations in 2000 to 3,959,560 hospitalizations in 2014 (11). In that study, persons with diabetes accounted for ~40% of all AKI hospitalizations, with absolute increases over time in AKI hospitalizations being larger among persons with diabetes than among persons without diabetes (11).

Diabetes Increases the Risk of AKI

Numerous other studies have drawn similar conclusions: that AKI is more common in persons with diabetes. For example, in an evaluation of data from 449,524 patients undergoing coronary artery bypass grafting (CABG) or valve surgery, the odds ratio (OR) for the requirement for postoperative dialysis was 2.17 (95% CI 2.03–2.33) for the presence of diabetes treated with insulin and 1.42 (95% CI 1.33–1.51) for the presence of diabetes treated with oral agents (12). Interestingly, among 36,106 patients from the SWEDEHEART register who underwent CABG between 2003 and 2013, AKI was more common in people with a diagnosis of type 1 diabetes (adjusted OR 4.89, 95% CI 3.82–6.25) than patients with type 2 diabetes (adjusted OR 1.27, 95% CI 1.16–1.40) in comparison with patients without diabetes (13). In a meta-analysis involving >1 million participants, low estimated glomerular filtration rates (eGFRs) and high urine albumin-to-creatinine ratios (ACRs) were associated with an increase in the risk of AKI, with hazard ratios (HRs) being generally higher among individuals with diabetes for any level of eGFR or ACR (14). This increase in AKI risk with diabetes appears to exist irrespective of the underlying etiology of the AKI event, being observed in patients developing AKI as a consequence of cardiac surgery, usage of certain medications, or sepsis or without an obvious precipitant (reviewed in Yu and Bonventre [15]). Furthermore, not only is AKI more common in persons with diabetes, but also if a person with diabetes develops AKI their outlook is worse as well. In one study, rates of dialysis-requiring AKI were approximately five times higher among persons with diabetes than among persons without diabetes (16), and whereas dialysis-requiring AKI rates appeared to plateau among individuals without diabetes, they have continued to increase in persons with diabetes (16). Finally, it is worth noting that the increase in risk of AKI in diabetes is not simply a factor of aging or premature aging. In fact, the effect of age on AKI risk in diabetes is not as straightforward as may be anticipated. For instance, among 3,471 patients with diabetes and community-acquired pneumonia, investigators observed a more graded relationship between reduced eGFR and risk of AKI in persons ≥80 years of age than in younger individuals (17). Similarly, in a registry study from Taiwan, comorbidities, interventions, and certain medications affected the risk of AKI in persons with diabetes in some age-groups but not in others (18).

Table 2—KDIGO staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 × baseline or ≥0.3 mg/dL (≥26.5 μmol/L) increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 × baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 × baseline, increase in serum creatinine to ≥4.0 mg/dL (≥353.6 μmol/L), initiation of renal replacement therapy, or, in patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

If the staging for serum creatinine and urine output differ, patients should be staged according to the criteria that put them in the highest stage. Adapted from KDIGO Clinical Practice Guideline for Acute Kidney Injury (6).

Why Does Diabetes Increase the Risk of AKI?

There are, of course, several reasons why diabetes may increase the risk of AKI (Fig. 1).

Chronic Kidney Disease Increases the Risk of AKI

Diabetes is the most common cause of chronic kidney disease (CKD) worldwide, and AKI is more common in people with CKD. Up to 2016, the global prevalence rate of CKD was ~3,732 cases per 100,000 persons, of which ~1,691 cases per 100,000 persons were attributable to diabetes (19). In turn, CKD independently increases the risk of AKI. For instance, one early study reported that the adjusted OR of dialysis-requiring "acute renal failure" in a cohort of hospitalized patients, in comparison with patients with a baseline eGFR ≥60 mL/min/1.73 m^2, was 1.95 (95% CI 1.66–2.30) for patients with a baseline eGFR 45–50 mL/min/1.73 m^2, 6.54 (95% CI 5.57–7.69) for patients with baseline eGFR 30–44 mL/min/1.73 m^2, 28.50 (95% CI 24.50–33.14) for patients with baseline eGFR 15–29 mL/min/1.73 m^2, and 40.07 (95% CI 33.75–47.48) for patients with a baseline eGFR <15 mL/min/1.73 m^2 (20). Interestingly, in that study the adjusted OR for

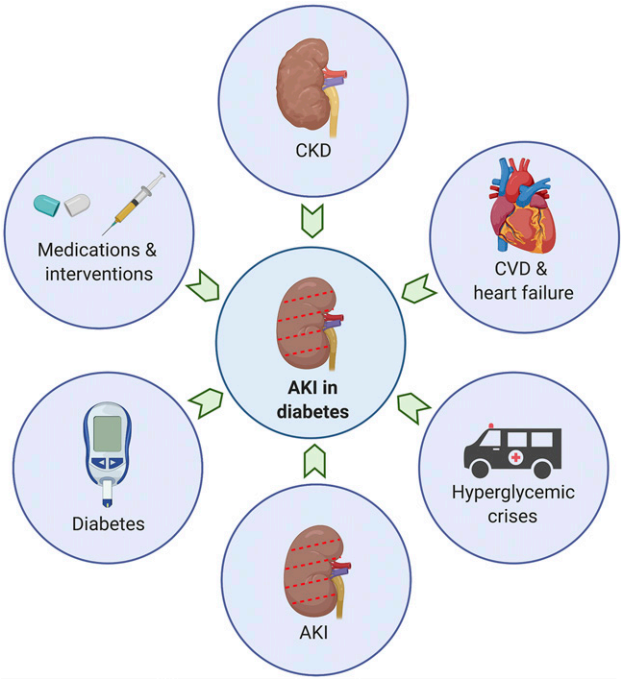

Figure 1—Causes of AKI in diabetes. Illustrating the major contributors to the increased risk of AKI in diabetes. These include CKD; CVD, including acute coronary artery syndromes and cardiac surgery; heart failure; hyperglycemic crises (DKA and HHS); AKI itself (predisposing to future episodes of AKI); diabetes itself (hyperglycemia); and sometimes medications used in the treatment of diabetes or its complications or in the investigation of comorbidities in persons with diabetes (e.g., radiocontrast).

dialysis-requiring acute renal failure was also increased for patients with documented proteinuria (2.89, 95% CI 2.41–3.47) and for patients with diabetes (2.08, 95% CI 1.75–2.47) (20). However, the high prevalence of CKD among persons with diabetes does not explain all of the increased risk of AKI.

Cardiovascular Disease and Heart Failure Increase the Risk of AKI

Diabetes also increases the risk of cardiovascular disease (CVD) and heart failure, and these conditions can themselves increase the risk of AKI. Approximately 40% of patients undergoing cardiac surgery have a diagnosis of diabetes (21), and the reported incidence of cardiac surgery–associated AKI varies widely, between 5 and 42%, according to the population being studied (22). In patients undergoing CABG, AKI developed in 26% of patients with heart failure (23), which is itself much more common in people with diabetes. Patients with coronary artery disease (CAD) may be exposed to contrast agents during the workup for stable CAD or in the treatment of acute coronary syndromes. In a retrospective analysis of >2,000 patients who underwent percutaneous coronary intervention, the incidence of AKI was 2.3% and the requirement for renal replacement therapy occurred in 0.3% of cases (24,25).

Hyperglycemic Crises Cause AKI

In addition to the long-term complications of diabetes, acute hyperglycemic complications of diabetes (i.e., diabetic ketoacidosis [DKA] or hyperosmolar hyperglycemic state [HHS]) can also increase the risk of AKI. In a retrospective study of 94 patients admitted to an intensive care unit with "severe DKA," 47 patients (50%) presented with AKI on admission (26). In a separate study of 165 children with type 1 diabetes hospitalized for DKA, 106 (64.2%) developed AKI, two of whom required hemodialysis (27). The incidence of AKI in patients with HHS has been less clearly defined. However, HHS often presents with profound dehydration, which predisposes to AKI, and HHS itself may be complicated by rhabdomyolysis, which increases the propensity to AKI development.

AKI Increases the Risk of AKI

Aside from the contributions to AKI risk of the acute and chronic complications of diabetes, AKI itself increases the risk of future episodes of AKI. For example, in a study of 11,863 AKI hospitalizations, 2,954 patients (25%) were hospitalized with recurrent AKI within 12 months of discharge (28). Similarly, in a retrospective cohort study of 38,659 hospitalized members of Kaiser Permanente Northern California, 11,048 patients experienced a second hospitalization that was complicated by AKI, occurring at a median of 0.6 years after first hospitalization (29). There are likely several causes of increased risk of future AKI after an episode of AKI. On the one hand, the occurrence of AKI in an individual identifies that individual, by definition, as someone at risk for AKI. On the other hand, there may also be cellular explanations. For instance, epigenetic processes provide a means by which a transient environmental insult can cause persistent cellular change, and epigenetic processes have recently been recognized as important players in both AKI and kidney repair (30).

Medications Used in the Management of Diabetes May Increase AKI Risk, but They May Also Reduce It

It is also possible that medications used in the management or investigation of people with diabetes may increase the risk of AKI. However, the actual contribution of medications to the increased incidence of AKI in diabetes is not as clear as may be expected. Renin-angiotensin-aldosterone system (RAAS) blockers are commonly used in the management of hypertension, for vascular protection, and to slow the progression of kidney disease in people with diabetes. During times of reduced renal perfusion, as occurs with hypovolemia or renal artery stenosis for instance, RAAS blockade may promote AKI development by reducing intraglomerular pressure through preferential vasodilatation of the efferent arteriole. However, data supporting a major role for RAAS blockers as causative factors in AKI development are surprisingly scant (31). For example, in a cohort study using the U.K. Clinical Practice Research Datalink (CPRD), that included 570,445 participants (303,761 prescribed an ACE inhibitor or angiotensin II

receptor blocker) and a median follow up of 4.1 years, the adjusted relative risk for AKI was only 1.12 (95% CI 1.07–1.18) (32). Dual renin-angiotensin system blockade does, however, increase AKI risk and is not recommended (33).

There has also been concern about use of sodium–glucose cotransporter 2 (SGLT2) inhibitors and risk of AKI, but the current evidence points in the contrary direction: that SGLT2 inhibition appears to be associated with a reduction in AKI events. This decrease in AKI risk has been borne out in three separate meta-analyses (HR 0.66, 95% CI 0.54–0.80 [34], OR 0.64, 95% CI 0.53–0.78 [35], or relative risk 0.59, 95% CI 0.39–0.89 [36], depending on individual study design). Similarly, in a propensity-matching analysis of two cohorts, investigators found no increase in the risk of AKI in patients with type 2 diabetes prescribed an SGLT2 inhibitor, with a trend toward reduced risk (37). Even in randomized controlled trials of individuals at higher risk of AKI, SGLT2 inhibition has not been found to be associated with an increased occurrence of AKI. For example, among participants in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, who had type 2 diabetes and albuminuric CKD (eGFR 30–89 mL/min/1.73 m^2 and urine ACR >300 mg/g [>33.9 mg/mmol], treated with RAAS blockade) the HR for AKI was 0.85 (95% CI 0.64–1.13) (38).

The presence of diabetes also predicts the likelihood of contrast-induced nephropathy in patients undergoing diagnostic or interventional procedures that involve the use of radiocontrast media (39). If contrast-induced nephropathy occurs in patients taking metformin, there may also be an increased risk of lactic acidosis. However, this risk is also now recognized to be quite low, and, as a result, recent society recommendations have been amended accordingly (40). In sum, the increased incidence of AKI in diabetes cannot simply be attributed to the use of medications or interventional agents that may be harmful to the kidneys on "sick days."

Diabetes Alone Predisposes to AKI

Finally, diabetes in its own right increases the risk of AKI. Mechanistically, this has been demonstrated in preclinical models. For example, in one notable study, mice with streptozotocin-induced diabetes or Akita diabetic mice each exhibited heightened susceptibility to increased tubule cell damage and programmed cell death caused by ischemia reperfusion injury (IRI) (41). In the same study, proximal tubule cells exposed to high glucose exhibited heightened apoptosis following depletion of ATP or exposure to severe hypoxia (41). Mechanistically, the authors identified activation of the intrinsic pathway of apoptosis characterized by mitochondrial Bax accumulation and cytochrome c release (41). Using chemical inhibition studies, short interfering RNA, and cell-specific knockout mice, the authors attributed activation of the intrinsic pathway of apoptosis to upregulation of p53 in tubule cells exposed to high glucose and ischemic insult (41). An earlier study in streptozotocin diabetic mice similarly reported that these animals exhibited heightened sensitivity to IRI, which the authors at the time speculated may be due to downregulation of bcl-2, which is antiapoptotic, and bone morphogenic protein-7 (BMP-7), which is antifibrotic and proregenerative (42). In a separate study, investigators reported that type 2 diabetic *db/db* mice exhibited augmented kidney damage in response to bilateral IRI, accompanied by upregulation of tumor necrosis factor-α (TNF-α) and Toll-like receptor 4 (TLR4), whereas a neutralizing anti–TNF-α antibody attenuated kidney injury (43). These studies point to roles for apoptotic or inflammatory pathways in increasing the propensity to AKI with diabetes. However, other mechanisms likely also contribute. For instance, studies using blood oxygen level–dependent MRI have reported diminished oxygenation of the kidneys in diabetes (44,45), which is likely to be mediated at least partly by a reduction in peritubular capillary number and density.

Does AKI Increase the Risk of CKD in Diabetes?

Given that AKI is more common in people with diabetes and diabetes is the most common cause of CKD across the globe, what then is the evidence that AKI contributes to CKD risk?

AKI Increases the Risk of CKD, End-Stage Kidney Disease, and Mortality

A wealth of epidemiological data generated over the past decade indicates not that AKI is a benign, self-limiting, and reversible condition but, rather, that an episode of AKI increases the risk of CKD, end-stage kidney disease (ESKD), and mortality and that this risk increases with each subsequent episode of AKI and with the severity of AKI. A systematic review and meta-analysis published in 2012 served to underscore the significance of the relationship between AKI and worsening long-term kidney function or ESKD (46). That report, which assimilated findings from 13 cohort studies, concluded a pooled HR of 8.8 for CKD in patients with AKI versus those without AKI (95% CI 3.1–25.5) and an HR for ESKD of 3.1 (95% CI 1.9–5.0) (46), with a graded relationship between severity of AKI and either CKD or ESKD (46). A more recent meta-analysis of data comprising >2 million participants reported similar associations; the HR for new or progressive CKD in patients with AKI was 2.67 (95% CI 1.99–3.58), the HR for ESKD was 4.81 (95% CI 3.04–7.62), and the HR for death was 1.80 (95% CI 1.61–2.02) (47). This association between AKI and CKD risk has also been reported specifically within populations with diabetes (48). For instance, among 3,679 individuals with diabetes studied over a 10-year period, the HR for stage 4 CKD for any episode of AKI versus no AKI was 3.56 (95% CI 2.76–4.71) (48), with the risk of stage 4 CKD approximately doubling for each subsequent episode of AKI (48). Among patients in the Veterans Health Administration, the adjusted relative risk of stage 3 CKD or higher after an episode of stage 1 AKI

was 1.35 (95% CI 1.31–1.38) for individuals with a preadmission diagnosis of diabetes (49). Aside from the risk of CKD and ESKD, among persons with diabetes, AKI has also been shown to be associated with an increased risk of death from both cardiovascular and noncardiovascular causes, major adverse cardiovascular events, heart failure hospitalization, lower-limb amputation, and carotid artery revascularization (50). In fact, diabetes not only increases the risk of CKD after AKI but, by meta-regression, has also been found to increase the relationship between AKI and mortality ($P = 0.03$) (47).

AKI Increases the Risk of Future Proteinuria

Recent prospective studies have also indicated that AKI is a risk factor for future proteinuria. For instance, in one retrospective cohort study of U.S. veterans hospitalized between 2004 and 2012, among 90,614 matched pairs with and without AKI, the OR for dipstick-positive proteinuria was 1.20–1.39 for AKI versus no AKI (51). This association was present regardless of whether the patient had an underlying diagnosis of diabetes (51). In a multivariable analysis of 2,048 participants enrolled from two prospective cohorts (the Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury [ASSESS-AKI] study and a subset of the Chronic Renal Insufficiency Cohort [CRIC]), an episode of hospitalization with AKI was associated with a 9% increase in urine protein-to-creatinine ratio (52). Furthermore, in a separate study of the ASSESS-AKI cohort, higher ACR post-AKI was predictive of kidney disease progression, defined as halving of eGFR or ESKD (HR 1.53 for each doubling of ACR, 95% CI 1.43–1.64) (53).

Experimental Studies Provide Insights Into How AKI May Cause Permanent Kidney Damage

Whereas epidemiological observations such as those summarized above serve to illustrate the association between AKI and long-term kidney dysfunction, they do not themselves prove causality. Here, like the earlier case of linking diabetes to increased AKI risk, we can turn to experimental models. For example, one group of investigators used Six2-Cre-LoxP technology to selectively activate expression of the simian diphtheria toxin receptor in mesenchyme-derived kidney epithelial cells (54). In this model, repeated exposure to diphtheria toxin caused acute injury specific to the S1 and S2 segments of the proximal tubule that was followed by inflammatory cell infiltration and tubule cell proliferation and recovery (54). However, repeating this exposure at weekly intervals for 3 weeks caused maladaptive repair with interstitial fibrosis, glomerulosclerosis, and rarefaction of the interstitial capillaries (54). This illustrates how inflammatory cells recruited to the kidney after AKI can release profibrotic cytokines, which can cause chronic scarring of the kidney. Rats with AKI induced by IRI have been reported to have persistent renal oxidative stress that enhances the deleterious effects of angiotensin II leading to enhanced renal vasoconstriction and tissue fibrosis (55), and the kidneys of rats subjected to prolonged, albeit transient, ischemia experience peritubular capillary dropout (56), which impairs tissue oxygenation. Persistent tubule epithelial cell dedifferentiation, premature senescence, and cell cycle arrest can also promote chronic tissue injury. Cellular senescence in response to acute injury may be of short-term benefit, facilitating tissue repair by enabling the targeted removal of damaged cells. However, senescent cells remain metabolically active, and they can secrete a number of cytokines and growth factors that engender a chronic inflammatory state and promote tissue fibrosis (e.g., interleukin-6 [IL-6], C-X-C motif ligand 1 [CXCL1], IL-8, plasminogen activator inhibitor-1 [PAI-1], and chemokine [C-C motif] ligand 2 [CCL2]), collectively termed the senescence-associated secretory phenotype or SASP (57–61). It has also been suggested that tubule cells may arrest at the G2/M stage of the cell cycle and that, in this state, these cells activate c-Jun NH_2-terminal kinase (JNK) signaling, which stimulates fibrotic cytokine production and the transition from AKI to CKD (62). Other mechanisms that may also contribute to CKD development after AKI include pericyte transdifferentiation, altered communication between the endothelial cells of the peritubular capillaries and tubule epithelial cells, and systemic hypertension (15,57,63) (Fig. 2).

What Can Be Done to Improve AKI Outcomes in Diabetes?

Unfortunately, despite the intensive research efforts of recent years, there are no effective treatments specifically for AKI beyond supportive care. This inertia has prompted two notable recent society initiatives: the International Society of Nephrology's 0by25 initiative, which has the ambitious goal of zero preventable deaths from AKI by 2025 (9), and the American Society of Nephrology's *AKI! Now* initiative, with the stated goal of promoting excellence in the prevention and treatment of AKI (64). One common emphasis of these initiatives is the avoidance of preventable episodes of AKI, given that many episodes of AKI are predictable. For example, in a chart review of 170 hospitalized patients with AKI, an avoidable cause was identified in 51 cases (65). Of these, the most commonly cited preventable causes were failure to administer saline prophylaxis for intravenous contrast when indicated (16 cases), suboptimal treatment of hemodynamic instability or hypertension (15 cases), inappropriate use of medications (9 cases), and use of multiple nephrotoxic agents (11 cases) (65). Other strategies to improve outcomes for individuals with AKI emphasize standardized process measures and alerts to facilitate the early identification of cases and prevention of AKI events. The 0by25 initiative stresses delineation of AKI under the "5 Rs," i.e., risk assessment, recognition, response, renal support, and rehabilitation (9). Other process measures include the accurate ascertainment of the incidence of AKI and its sequelae, increasing awareness of AKI risk, and use of electronic alert

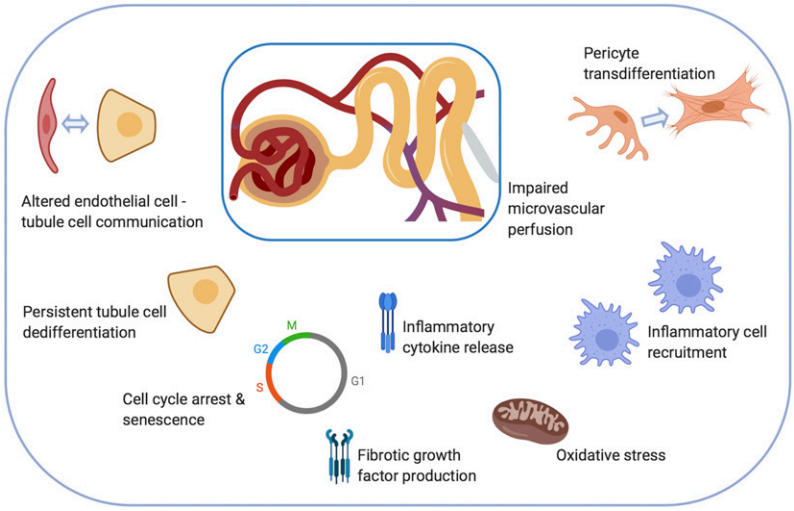

Figure 2—Mechanisms by which AKI can lead to CKD. Cellular and molecular mechanisms that promote transition from AKI to CKD include the following: inflammatory cell recruitment and retention, release of proinflammatory cytokines and profibrotic growth factors by tubule epithelial cells with resultant extracellular matrix deposition, persistent oxidative stress, cell-cycle arrest in tubule epithelial cells and stress-induced premature senescence, persistent tubule epithelial cell dedifferentiation, altered communication between endothelial cells of the peritubular capillaries and tubule epithelial cells, pericyte transdifferentiation, and impaired microvascular perfusion.

systems (9,64). Indeed, automated electronic alert systems have shown particular promise. For example, one such system based on AKIN and RIFLE criteria resulted in 59,921 alerts related to 15,550 different patients over a 2-year period, 50% of which were issued within 24 h of admission (66).

Novel Biomarkers Aid in the Early Identification of AKI

Although little progress has been made to date in terms of the development of specific treatments for AKI, there have been important advances in the use of biomarkers that facilitate the early prediction of AKI risk. Most urinary biomarkers of AKI fall into one of three categories: *1*) those that are freely filtered by the kidney glomerulus and endocytosed within the proximal tubule, this reuptake process being impaired in AKI (e.g., β2-microglobulin); *2*) those that are constitutively expressed by proximal tubule cells and released into the urinary filtrate if AKI occurs (e.g., N-acetyl β-glucosaminidase [NAG]); and *3*) those that are de novo expressed by tubule epithelial cells following AKI and released into the urine (e.g., neutrophil gelatinase-associated lipocalin [NGAL] and kidney injury molecule-1 [KIM-1]) (67). In 2013, a new biomarker was discovered that outperformed all other biomarkers of AKI, including NGAL and KIM-1 (68). This biomarker is the urinary level of the arithmetic product of tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) (68). Urine [TIMP-2] · [IGFBP7] was identified from a screen of 340 candidate proteins selected through hypotheses based on AKI pathophysiology, in which TIMP-2 and IGFBP7, both inducers of G_1 cell-cycle arrest, were the top two performing biomarkers, and in which, in a validation cohort (the Sapphire study), urine [TIMP-2] · [IGFBP7] had an area under the curve of 0.80 for development of stage 2 or 3 AKI within 12 h of measurement (68). The predictive ability of the test has subsequently been confirmed in several other studies, and a commercial assay based on these markers (NephroCheck) was approved by the U.S. Food and Drug Administration in 2014. The emergence of the [TIMP-2] · [IGFBP7] biomarker has led to renewed interest in the role of cell-cycle arrest in the pathogenesis of AKI. However, animal models have recently challenged the view that TIMP-2 and IGFBP7 are mechanistically involved in AKI-induced cell-cycle arrest, with absence of transcriptional changes observed for either biomarker (67). This suggests instead that increased urine levels of TIMP-2 and IGFBP7 are most likely caused by increased filtration, decreased tubule absorption, and proximal tubule leakage of translated proteins (67). Whereas patients with diabetes have been included in studies of [TIMP-2] · [IGFBP7], no studies published to date have examined the utility of the assay specifically within populations with diabetes.

Looking Toward the Future for AKI in Diabetes

A workshop convened by the National Institute of Diabetes and Digestive and Kidney Diseases, "AKI Outcomes: Overcoming Barriers in AKI," identified several challenges and opportunities in the search for new treatments for AKI (69). Highlights from this workshop include a recognition of the heterogeneity of AKI and a resulting need to define specific AKI endophenotypes. This would facilitate a "reverse translational medicine approach" whereby clinical trials could be envisioned according to particular patient subpopulations and the appropriate end points for these populations. Then animal models could be developed that

more accurately recapitulate these subpopulations (69), replacing existing animal models that lack the complexity through which AKI episodes typically occur in patients. More immediately, according to ClinicalTrials.gov, there are almost 100 AKI interventional trials that are recruiting, several of which are using novel therapeutic approaches including ANG-3777, a hepatocyte growth factor mimetic (clinical trial reg. no. NCT02771509); SBI-101, a biologic/device combination that uses allogeneic human mesenchymal stromal cells (NCT03015623); nicotinamide and pterostilbene (NCT04342975); berberine (NCT02808351); and QPI-1002, a p53-directed siRNA (NCT03510897). One of these studies is specifically testing its intervention in participants with diabetes (NCT02808351), and others include diabetes among the risk factors listed in the inclusion criteria (NCT02771509 and NCT03510897). Whether these or any of the other studies examining other strategies or repurposing opportunities in AKI will effectively improve outcomes for patients remains to be determined.

What Defines a Diabetes Complication?

In closing, let us to return to the question as to whether AKI is a bona fide complication of diabetes. A diabetes complication is a health problem that occurs because of diabetes. Complications can be subdivided in different ways, for instance, acute complications (e.g., DKA and hypoglycemia) and chronic complications (e.g., nephropathy, retinopathy, or neuropathy). Among the long-term complications of diabetes, health problems were historically classified as being "microvascular" or "macrovascular." Alternatively, diabetes complications can be subdivided according to their specificity for diabetes. Diabetic nephropathy (that is characterized by the classical histopathological Kimmelstiel-Wilson nodule) or diabetic retinopathy, by way of example, are complications that are specific to diabetes. Atherosclerosis, heart failure, fractures, or cataract, for instance, are also complications of diabetes. However, these conditions also occur in people without diabetes; diabetes increases the risk that they will occur. In this respect, AKI fulfills all the conditions for being considered a complication of diabetes. Like fractures, AKI often requires a precipitant. However, should a precipitating event occur, AKI is substantially more likely to occur if a person also has diabetes. It is hoped that inclusion of AKI in the expanding list of diabetes complications will help shine the spotlight on the problem and galvanize efforts to improve outcomes for persons with diabetes who are at risk for AKI or who are affected by AKI and its sequelae.

Summary

In summary, as we move into a new decade and as our understanding of the long-term risks of diabetes has evolved, so too has our understanding of the myriad of challenges that diabetes and its complications may bring. AKI is a complication of diabetes that is not a benign and reversible condition. Rather, it increases the risk of future episodes of AKI, CKD, ESKD, major adverse cardiovascular events, and all-cause mortality. Current strategies to improve outcomes in AKI should be focused on early identification and mitigation, use of supportive measures, and removal of any precipitants. Advances have been made in the early prediction of AKI, although the development of specific therapies for AKI in persons with or without diabetes has stalled. With the exception of glucose control, RAAS blockade, and, more recently, SGLT2 inhibition, most treatments of kidney disease in diabetes in clinical trials have been disappointing. These trials are costly and time-consuming, and they often require a large number of patients to accrue events. Given the evolving contribution of AKI to adverse outcomes in diabetes, a case could be made that drug development for this acute complication may offer a better return on investment. A better understanding of the pathobiology of AKI in persons with diabetes and in experimental models may open up avenues for the development of new treatments. In the meantime, practitioners should be vigilant about the risk of AKI in persons with diabetes and the consequences of its occurrence.

Acknowledgments. Figures were created with BioRender (BioRender.com).
Funding. Research in the Advani Laboratory is supported by grants from the Canadian Institutes of Health Research (PJT153284 and PJT166083), the Heart and Stroke Foundation of Canada (G-17-0018231), the Banting & Best Diabetes Centre, and the RDV Foundation. A.A. is a recipient of a Diabetes Investigator Award from Diabetes Canada and is the Keenan Chair in Medicine at St. Michael's Hospital and University of Toronto.
Duality of Interest. A.A. has received research support from Boehringer Ingelheim and AstraZeneca; has participated in advisory boards for Abbott, Dexcom, Boehringer Ingelheim/Eli Lilly, and Novo Nordisk; and has received an unrestricted educational grant from Eli Lilly. No other potential conflicts of interest relevant to this article were reported.

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