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Preface: Diabetic Chronic Kidney Disease: When the Other Shoe Drops **xi**

Mark E. Williams

Epidemiology of Diabetic Kidney Disease **1**

Anne T. Reutens

Diabetes currently affects 8.3% of the world's adults and will increase in prevalence in future decades. Diabetic kidney disease is a leading cause of end stage renal disease (ESRD) and health care expenditure. Diabetic kidney disease can develop along an albuminuric or non-albuminuric pathway. The risks of death from all causes and from cardiovascular disease increase with lower glomerular filtration rates. For those with albuminuria, the risks of ESRD and of all-cause mortality and cardiovascular mortality increase with higher levels of albumin excretion. Survival has improved compared to outcomes from the 1980s, and progression to ESRD is now more common than premature death. This chapter reviews the epidemiology of diabetic kidney disease in type 1 and type 2 diabetes.

Clinical Manifestations and Natural History of Diabetic Kidney Disease **19**

Eberhard Ritz

Renal failure in type 2 diabetes has been termed "a medical catastrophe of worldwide dimension". In 2001, we found in our unit that 49% of incident patients requiring maintenance hemodialysis had diabetes (i.e. 98/million population/year), 6% of whom had type 1 and most (94%) had type 2 diabetes, i.e. more than the than reported frequency in Germany (approximately 35% of incident patients). The frequency is underestimated because hyperglycemia is often lost in the preterminal phase when diabetic patients lose weight and fasting hyperglycemia.

The Pathogenesis and Management of Hypertension in Diabetic Kidney Disease **31**

Peter N. Van Buren and Robert D. Toto

Hypertension is one of the hallmark features of diabetic kidney disease. It contributes to both the progression of kidney disease and the risk for cardiovascular events in these patients. Although lowering blood pressure is critical in managing diabetic kidney disease, the ability to achieve this goal is complicated by the complexity of blood pressure regulation in these patients related to both extracellular volume expansion and increased vasoconstriction. This review includes a discussion of our current understanding of the etiology of hypertension in patients with diabetic kidney disease and an update of the most current clinical trials investigating anti-hypertensive interventions.

Nonproteinuric Diabetic Nephropathy: When Diabetics Don't Read the Textbook **53**

Jamie P. Dwyer and Julia B. Lewis

Diabetic nephropathy (DN) refers to the structural and functional changes in the kidneys of patients with diabetes mellitus (type 1 or 2). A subset of

patients with presumed DN may not have overt proteinuria as a prerequisite to renal failure, contrary to the classical paradigm. No animal model fully recapitulates the human subset. All studies on this subject are observational and most lack biopsy data. Many mechanisms have been postulated, including use of renin-angiotensin system agents, recurrent bouts of acute kidney injury, genetic predisposition, and renal lesions other than DN. A well-designed biopsy study and a series of intervention trials are needed to fully understand this entity.

Obesity and Diabetic Kidney Disease

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Christine Maric-Bilkan

Obesity and diabetes are major health concerns worldwide. Along with other elements of the metabolic syndrome, including hypertension, they contribute to the development and progression of renal disease, which, if not treated, may lead to end-stage renal disease (ESRD). Although early intervention and management of body weight, hyperglycemia, and hypertension are imperative, novel therapeutic approaches are also necessary to reduce the high morbidity and mortality associated with renal disease. This review provides perspectives regarding the mechanisms by which obesity may lead to ESRD and discusses prevention strategies and treatment of obesity-related renal disease.

Diabetic Kidney Disease in Elderly Individuals

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Mark E. Williams

Chronic kidney disease (CKD) complicates diabetes and also has an increased prevalence in elderly individuals. Particularly in those older than 60 years, the most common cause of CKD and end-stage renal disease in the United States is diabetic kidney disease. This growing population represents unique challenges in multidisciplinary medical management. Elderly diabetic patients with CKD may be underserved with regard to fundamental standards of care like the role of glucose control, hypertension management, and the use of renin-angiotensin blocking agents. Current management therefore needs to be reassessed in terms of the special needs of this growing population.

The Genetic Risk of Kidney Disease in Type 2 Diabetes

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Marcus G. Pezzolesi and Andrzej S. Krolewski

In this review, the authors discuss the major approaches being used to identify diabetic nephropathy (DN) susceptibility genes in type 2 diabetes (T2D) and highlight the salient findings from studies whereby these approaches have been implemented. The recent advent of next-generation sequencing technology is beginning to impact DN gene mapping strategies. As the field moves forward, family based approaches should greatly facilitate efforts to identify variants in genes that have a major effect on the risk of DN in T2D. To be successful, the ascertainment and comprehensive study of families with multiple affected members is critical.

Pancreas Transplantation and Reversal of Diabetic Nephropathy Lesions

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Michael Mauer and Paola Fioretto

Pancreas transplantation is the only available treatment that has restored long-term (10 or more years) normoglycemia without the risks of severe

hypoglycemia, allowing testing of the reversibility of diabetic nephropathy lesions. The authors studied renal structure before and 5 and 10 years after pancreas transplantation in nonuremic patients with long-term type 1 diabetes, with established diabetic nephropathy lesions at baseline. Diabetic glomerular lesions were not significantly changed at 5 years but were dramatically improved after 10 years, with most patients' glomerular structure returning to normal at the 10-year follow-up. These studies also showed that tubulointerstitial remodeling was also possible.

Potential New Treatments for Diabetic Kidney Disease

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Deanna S. Kania, Cory T. Smith, Christy L. Nash, Jasmine D. Gonzalvo, Andrea Bittner, and Brian M. Shepler

Diabetic kidney disease is a complex pathologic process that involves many biochemical associations. As our understanding of this processes deepens, potential new targets for drug therapy become apparent. There are several mechanisms by which medications may be able to inhibit or slow the progression of kidney disease. Existing medications and entirely new compounds have been studied in human subjects that have antifibrotic and antioxidant effects as well as the ability to bind with and antagonize specific receptors known to contribute to the deleterious effects observed in diabetic kidney disease patients. While most potential new drug therapies remain highly experimental, there is a growing body of data from clinical trials show that many new drugs may eventually lead to new standards for drug treatment in diabetic kidney disease. Potential new drug therapies discussed include antifibrotic agents, antioxidant agents, ET-a receptor antagonists and other compounds with non-specific or multi-faceted mechanisms of action such as paricalcitol, ruboxistaurin, palosuran, allopurinol, and fasudil.

Diabetes Management in the Kidney Patient

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Rajesh Garg and Mark E. Williams

Hyperglycemia management in chronic kidney disease (CKD) patients presents difficult challenges, partly due to the complexity involved in treating these patients, and partly due to lack of data supporting benefits of tight glycemic control. While hyperglycemia is central to the pathogenesis and management of diabetes, hypoglycemia and glucose variability also contribute to outcomes. Multiple agents with different mechanisms of action are now available; some can lower glucose levels without the risk of hypoglycemia. This article reviews metabolic changes present in kidney impairment/failure, current views about glycemic goals, and treatment options for the diabetic patient with CKD.

Comanagement of Diabetic Kidney Disease by the Primary Care Provider and Nephrologist

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Brendan T. Bowman, Amanda Kleiner, and W. Kline Bolton

Diabetic kidney disease (DKD) is a common disorder, and few patients achieve current therapeutic targets. Careful collaboration between all health care providers and the creation of disorder-specific health care systems seem to offer the best opportunity for improving the management and clinical outcomes of these patients. This article explores the barriers

to effective collaboration between physicians in the management of patients with DKD, attitudes and perceptions of physicians toward collaborative management, and the physiologic challenges in patients with DKD that would warrant specialist involvement in their care. A model for collaborative DKD care delivery is also proposed.