RENAL COMPLICATIONS

Not only do the kidneys participate in signaling the onset of type 1 diabetes mellitus, but they also are vulnerable to severe damage over the long-term course of the disease.

One of the most common presenting symptoms of type 1 diabetes is polyuria, which occurs when hyperglycemia is so great that the amount of glucose entering the nephron exceeds the amount that can be reabsorbed in the proximal tubule. What follows is osmotic diuresis, in which the solute (glucose) is trapped in the tubule lumen and causes water to remain in the lumen and thus be excreted rather than reabsorbed. The ensuing dehydration that occurs is compensated by the patient's intense thirst, or polydipsia.

Approximately 30-40% of patients with type 1 diabetes and 20-30% of patients with type 2 diabetes will develop diabetic nephropathy. Although the reasons for developing this disorder have not been completely elucidated, evidence indicates that both genetic and environmental factors may play a role. Poor control of one's diabetes appears to be a particularly significant risk factor for diabetic nephropathy, with hyperglycemia being the proposed culprit. Consistently high blood sugar favors glycosylation, resulting in the formation of structures called advanced glycosylation endproducts (AGEs). Because these are highly reactive species, they contribute to cross-linking of proteins in the mesangial matrix, as well as to thickening of the glomerular basement membrane – two of the principal features of diabetic nephropathy. Without the proper management, diabetic nephropathy can progress to end-stage renal disease, a major source of diabetes-related morbidity and mortality.

More information about the renal complications of diabetes is discussed in the following articles:

History:
Patients with new-onset diabetes (especially type 1, in which blood glucose levels can be very high) often note polyuria (as a downstream result of hyperglycemia) and polydipsia. Patients with long-standing diabetes may present with advanced renal disease and have symptoms of uremia: nausea and vomiting. They may also complain of decreased urine output. If renal function falls to less than 10% of normal, neurological changes of poor cognitive function, uremic encephalopathy, and involuntary jerking movements in the hands (asterixis) may occur.

Physical Exam:
In patients with advanced kidney disease who have decreased urine output, there may be edema and hypertension from the buildup of fluid. Because of the disturbances to one's blood chemistry from severe renal failure, patients may have asterixis and/or decreased cognitive abilities. Uremic encephalopathy may even cause coma.

Tests:
In a patient with suspected diabetic nephropathy, the first line of tests will be blood and urine tests. While urinalysis may show glycosuria if the serum glucose is high enough, the first sign of diabetic nephropathy is persistent microalbuminuria, which is discovered by collection of a 24-hour urine sample. Blood tests will also be performed: the serum creatinine level is a standard barometer of kidney function; the blood urea nitrogen (BUN) level indicates the presence of azotemia/uremia.

The three major histologic changes in the glomeruli in diabetic nephropathy include: mesangial expansion; glomerular basement membrane thickening; and glomerular sclerosis. Glomerular sclerosis may have a nodular appearance, referred to as a Kimmelstiel-Wilson lesion (or Kimmelstiel-Wilson bodies). Observe these nodular deposits in the figure below.

Treatment:
Whether early in the onset of diabetes, or after the presence of diabetic nephropathy, it is always critical to emphasize to patients the importance of **controlling their blood sugar**. Even in patients with established diabetic nephropathy, glycemic control and lipid control can partially reverse glomerular hypertrophy and decrease the amount of protein excreted in the urine. Thus, although for many patients controlling their diabetes is a very demanding task, the benefits of meeting this challenge are plentiful.

In terms of pharmacological therapy for the patient with diabetic nephropathy, **ACE inhibitors** or **Angiotensin Receptor Blockers (ARBs)** can not only treat the hypertension that results from the kidney damage, but they can also reduce the amount of proteinuria and actually slow the progression of nephropathy. For these reasons, patients with microalbuminuria are typically prescribed one of these medications.

Screening for microalbuminuria should be done at five years after the diagnosis of type 1 diabetes since the date of diabetes onset is usually clear (patients present to a physician with initial symptoms) and nephropathy is uncommon until at least five years post-onset. In contrast, because many individuals with type 2 diabetes will have had hyperglycemia for years before presenting to a physician, some experts recommend that screening in these individuals should begin immediately upon the diagnosis of type 2 diabetes.

**Self Assessments:**
A 19 year-old college student developed type 1 diabetes at age 14. You now see him in your primary care clinic. To decrease his future risk of developing kidney failure from diabetic nephropathy, you should:

A. Encourage strict glycemic control  
B. Initiate annual urine screening for microalbuminuria  
C. Both A and B

*Explanations:*
A. Incorrect  
B. Incorrect  
C. Correct! Strict glycemic control is extremely important to decrease one’s risk of diabetic nephropathy. In addition, five years after the diagnosis of type 1 diabetes, annual screening for microalbuminuria is recommended to catch early signs of diabetic nephropathy, so that medical and lifestyle interventions can keep the patient from developing kidney failure.

Ten years later, this same patient (he is now 29 years old) reestablishes care with you. His diabetes has been under variable control. A urinalysis reveals proteinuria and glycosuria. Which of the following is MOST LIKELY occurring in his kidneys?

A. Thinning of the glomerular basement membrane  
B. The formation of advanced glycosylation endproducts (AGEs)  
C. Retraction of the mesangial matrix  
D. Absence of nodular deposits because he does not yet have end-stage renal disease

*Explanations:*
A. Incorrect. Diabetic nephropathy involves *thickening* of the glomerular basement membrane.  
B. Correct! Consistently high blood sugar is believed to produce advanced glycosylation endproducts (AGEs), highly reactive species that damage the mesangial matrix and glomerular basement membrane.  
C. Incorrect. Diabetic retinopathy involves mesangial expansion.  
D. Incorrect. Kimmelstiel-Wilson bodies indicate glomerular sclerosis, one of the primary features of diabetic nephropathy.