Understanding the Kidneys' Role in Blood Glucose Regulation

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Abstract

While not traditionally discussed, the kidneys' contributions to maintaining glucose homeostasis are significant and include such functions as release of glucose into the circulation via gluconeogenesis, uptake of glucose from the circulation to satisfy their energy needs, and reabsorption of glucose at the level of the proximal tubule. Renal release of glucose into the circulation is the result of glycogenolysis and gluconeogenesis, respectively involving the breaking down and formation of glucose-6-phosphate from precursors (eg, lactate, glycerol, amino acids). With regard to renal reabsorption of glucose, the kidneys normally retrieve as much glucose as possible, rendering the urine virtually glucose free. The glomeruli filter from plasma approximately 180 grams of D-glucose per day, all of which is reabsorbed through glucose transporter proteins that are present in cell membranes within the proximal tubules. If the capacity of these transporters is exceeded, glucose appears in the urine. The process of renal glucose reabsorption is mediated by active (sodium-coupled glucose cotransporters) and passive (glucose transporters) transporters. In hyperglycemia, the kidneys may play an exacerbating role by reabsorbing excess glucose, ultimately contributing to chronic hyperglycemia, which in turn contributes to chronic glycemic burden and the risk of microvascular consequences. This article provides an extensive review of the kidneys' role in normal human physiology, the mechanisms by which they contribute to glucose regulation, and the potential impact of glucose imbalance on the kidneys.

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For author information and disclosures, see end of text.

Published studies over the last 60 years have provided considerable evidence regarding the ability of the kidneys to make and release glucose under various physiologic conditions. Yet traditionally, the kidneys have not been considered an important source of glucose (except during acidosis or after prolonged fasting), with most clinical discussions on glucose dysregulation centering on the intestine, pancreas, liver, adipose tissue, and muscle.[1-3] More recently, however, the full significance of the kidneys' contribution to glucose homeostasis, under both physiologic and pathologic conditions, has become well recognized, and is thought to involve functions well beyond glucose uptake and release. Besides the liver, the kidney is the only organ capable of generating sufficient glucose (gluconeogenesis) to release into the circulation, and it is also responsible for filtration and subsequent reabsorption or excretion of glucose.[2-4] These findings have provided considerable insight into the myriad of pathophysiologic mechanisms involved in the development of hyperglycemia and type 2 diabetes mellitus (T2DM).[5,6] This article provides a review of the kidneys' role in normal human physiology, the mechanisms by which they contribute to glucose regulation, and the potential impact of glucose imbalance on the kidneys.

Overview of Renal Physiology

The kidneys are essentially designed to filter large quantities of plasma, reabsorb substances that the body must conserve, and secrete substances that must be eliminated. These basic functions are critical to regulation of fluid and electrolyte balance, body fluid osmolality, acid-based balance, excretion of metabolic waste and foreign chemicals, arterial pressure, hormone secretion, and, most relevant to this discussion, glucose balance.[7,8] The 2 kidneys produce a total of approximately 120 mL/min of ultrafiltrate, yet only 1 mL/min of urine is produced. The basic urine-forming unit of the kidney is the nephron, which serves to filter water and small solutes from plasma and reabsorb electrolytes, amino acids, glucose, and protein. The nephron, of which there are approximately 1 million in each kidney, consists of a filtering apparatus (the glomerulus) that is connected to a long tubular portion that reabsorbs and conditions the glomerular ultrafiltrate. Fluid filtered from the glomerular capillaries flows into the tubular portion, which is made up of a proximal tubule, the Loop of Henle, and

the distal tubule, all of which assist in reabsorbing essential substances and converting filtered fluid into urine.[7]

Evaluation of renal function is an important part of care, and with that, creatinine clearance (CrCl) or glomerular filtration rate (GFR), most frequently estimated (eGFR), are considered most useful in determining the degree of renal insufficiency and the stage of chronic kidney disease in accordance with the National Kidney Foundation classification system. Since alterations in all renal functions (ie, filtration, secretion, reabsorption, endocrine and metabolic function) have been associated primarily with GFR, this quantitative index may be used to measure any functional changes that result from kidney-related disease progression, therapeutic intervention, or toxic insult.[9]

Mechanisms of Glucose Homeostasis in the Kidneys

As described in greater detail in the first article in this supplement, maintenance of glucose homeostasis is crucial in preventing pathological consequences that may result from hyperglycemia or hypoglycemia. Chronically uncontrolled hyperglycemia leads to a higher risk of macrovascular and microvascular complications, such as cardiovascular disease, nephropathy, neuropathy, and retinopathy.[10] Hypoglycemia, on the other hand, may lead to a myriad of central nervous system complications (eg, confusion, behavioral changes, seizures, loss of consciousness, and even death), since the brain is the body's largest consumer of glucose in the fasting or "postabsorptive" state.[10,11] Maintenance of glucose homeostasis involves several complementary physiologic processes, including glucose absorption (in the gastrointestinal tract), glycogenolysis (in the liver), glucose reabsorption (in the kidneys), gluconeogenesis (in the liver and kidneys), and glucose excretion (in the kidneys).[10,12]

As alluded to previously, the kidneys are capable of synthesizing and secreting many important hormones (eg, renin, prostaglandins, kinins, erythropoietin) and are involved in a wide variety of metabolic processes such as activation of vitamin D_3, gluconeogenesis, and metabolism of numerous endogenous compounds (eg, insulin, steroids).[9] With respect to renal involvement in glucose homeostasis, the primary mechanisms include release of glucose into the circulation via gluconeogenesis, uptake of glucose from the circulation to satisfy the kidneys' energy needs, and reabsorption of glucose at the level of the proximal tubule.[13]

Glycogenolysis and Gluconeogenesis

Renal release of glucose into the circulation is the result of glycogenolysis and gluconeogenesis. Glycogenolysis involves the breakdown of glycogen to glucose-6-phosphate from precursors (eg, lactate, glycerol, amino acids) and its subsequent hydrolysis (via glucose-6-phosphatase) to free glucose. Conversely, gluconeogenesis involves formation of glucose-6-phosphate from those same precursors and subsequent conversion to free glucose. Interestingly, the liver and skeletal muscles contain most of the body's glycogen stores, but only the liver contains glucose-6-phosphatase. As such, the breakdown of hepatic glycogen leads to release of glucose, whereas the breakdown of muscle glycogen leads to release of lactate. Lactate (generated via glycolysis of glucose by blood cells, the renal medulla, and other tissues) may be absorbed by organs and reformed into glucose.[2]

With regard to glucose utilization, the kidney may be perceived as 2 separate organs, with glucose utilization occurring predominantly in the renal medulla and glucose release limited to the renal cortex. These activities are separated as a result of differences in the distribution of various enzymes along the nephron. To this point, cells in the renal medulla (which, like the brain, are obligate users of glucose) have significant glucose-phosphorylating and glycolytic enzyme activity, and can therefore phosphorylate and accumulate glycogen. However, since these cells lack glucose-6-phosphatase and other gluconeogenic enzymes, they cannot release free glucose into the circulation. On the other hand, renal cortex cells do possess gluconeogenic enzymes (including glucose-6-phosphatase), and therefore can make and release glucose into the circulation. But because these cells have little phosphorylating capacity, they cannot synthesize glycogen.[2]

The magnitude of renal glucose release in humans is somewhat unclear, with inconclusive evidence regarding the contribution of the kidneys to total body gluconeogenesis.[4] One analysis of 10 published studies concluded that the renal contribution to total body glucose release in the postabsorptive state is approximately 20%. Based on the assumption that gluconeogenesis accounts for approximately half of all circulatory glucose release during the fasting state, renal gluconeogenesis is projected, although not conclusively proven, to potentially be responsible for approximately 40% of all gluconeogenesis.[2] Taking into consideration the potential contribution of renal gluconeogenesis, the kidneys appear to play a substantial role in overall glucose release in normal as well as pathophysiologic states (eg, hepatic insufficiency, counterregulation of hypoglycemia). To this point, evidence suggests that in patients with T2DM, renal glucose release is increased in both the postprandial and postabsorptive states, implicating the kidneys' contribution to the hyperglycemia that characterizes this condition.[4] In one study, a 3-fold increase in renal glucose release was observed in patients with diabetes versus those without.[14] In contrast, hepatic glucose

Table. Distribution of Several Major GLUT and SGLT Transporters[13]

Transporter (Gene)	Distribution
SGLT1 (SLC5A1)	Intestine, renal proximal tubule (S3), brain, heart, trachea
SGLT2 (SLC5A2)	Renal proximal tubule (S1 and S2–S1 segment is where a majority of glucose reabsorption is mediated)
GLUT1 (SLC2A1)	Widespread; highest levels in erythrocytes and vascular endothelium
GLUT2 (SLC2A2)	Liver, pancreas, intestine, renal proximal tubule

GLUT indicates facilitated glucose transporter; SGLT, sodium-coupled glucose cotransporter.
Adapted from Wright EM, Hirayama BA, Loo DF. *J Int Med.* 2007;261(1):32-43.

release increased by only 30% in the diabetic state. Potential mechanisms involved in excessive renal glucose release in T2DM include fasting gluconeogenesis, decreased postprandial insulin release, insulin resistance (known to suppress renal/hepatic insulin release), increased free fatty acid (FFA) concentrations (FFAs stimulate gluconeogenesis), greater availability of gluconeogenic precursors, and increased glycogenolysis.[3] Again, it is clear that there is a renal contribution to glucose output in the body, but the actual contribution in individual patients with T2DM is still controversial.

Glucose Reabsorption

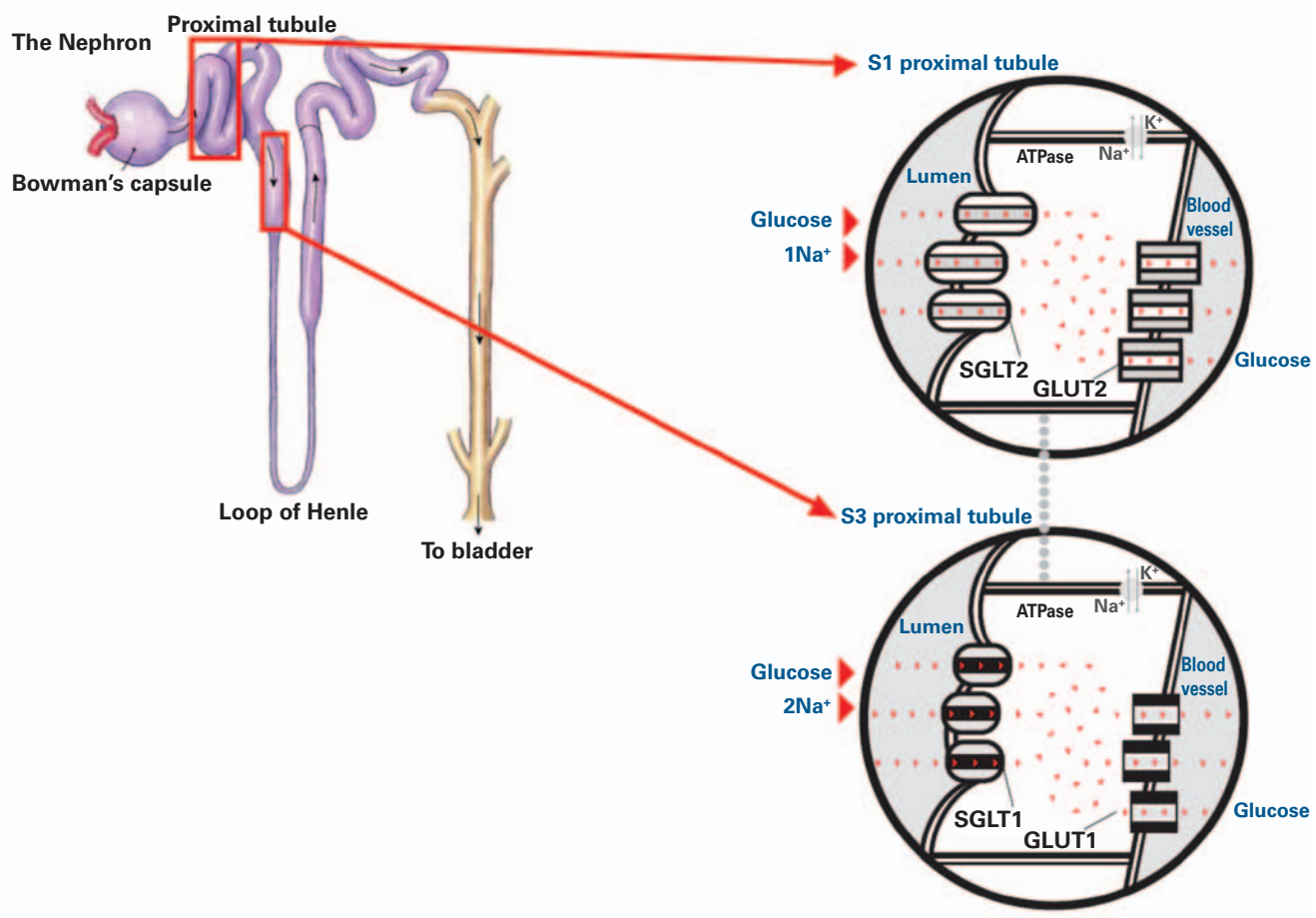
In addition to their important role in gluconeogenesis, the kidneys contribute to glucose homeostasis by filtering and reabsorbing glucose. Under normal conditions, the kidneys retrieve as much glucose as possible, rendering the urine virtually glucose free. The glomeruli filter from plasma approximately 180 grams of D-glucose per day, all of which is reabsorbed through glucose transporter proteins that are present in cell membranes within the proximal tubules.[4] If the capacity of these transporters is exceeded, glucose appears in the urine. This maximum capacity, known as the tubular maximum for glucose (TmG), ranges from 260 to 350 mg/min/1.73 m^2 in healthy adults and children, and corresponds to a plasma glucose level of approximately 200 mg/dL.[4] Once the TmG (the threshold) is reached and transporters are unable to reabsorb all the glucose (as in T2DM), glucosuria ocurrs.[7,15] The correlation between the degree of hyperglycemia and degree of glucosuria becomes linear when blood glucose concentrations have increased beyond a threshold.[4] It should be noted that slight differences between individual nephrons and the imprecise nature of biological systems may alter this linear concentration/reabsorption curve, as indicated by a splay from the theoretical as the TmG is approached.[4] As such, glucosuria may potentially develop before the expected TmG is reached. Glucosuria may also occur at lower plasma glucose concentrations in certain conditions of hyperfiltration (eg, pregnancy), but as a consequence of hyperfiltration rather than significant hyperglycemia.[12]

Renal Glucose Transporters

The transport of glucose (a polar compound with positive and negative charged areas, making it soluble in water) into and across cells is dependent on specialized carrier proteins in 2 gene families: the facilitated glucose transporters (GLUTs) and the sodium-coupled glucose cotransporters (SGLTs). These transporters control glucose transport and reabsorption in several tissue types, including the proximal renal tubule, small intestine, blood-brain barrier, and peripheral tissues (**Table**).[13,16] GLUTs are involved in the passive transport of glucose across cell membranes, facilitating its downhill movement as it equilibrates across a membrane. SGLTs, on the other hand, mediate active transport of glucose against a concentration gradient by means of cotransport with sodium. Of the various SGLT proteins expressed in the kidneys, SGLT2 is considered most important; based on animal studies, it is responsible for reabsorbing 90% of the glucose filtered at the glomerulus.[4] SGLT1 contributes to the other 10% of glucose reabsorbed in the proximal tubule. This predominant role of SGLT2 in renal reabsorption of glucose raises the prospect of therapeutically blocking this protein in patients with diabetes. Of the various GLUT proteins expressed in the kidneys, GLUT2 is the major transporter, releasing into circulation the glucose reabsorbed by SGLTs in the proximal tubular cells (**Figure**).[4,17]

In examining disorders involving renal glucose transport, gene mutations within SGLTs lead to inherited disorders of renal glucosuria, including familial (primary) renal glucosuria (FRG) and glucose-galactose malabsorption (GGM). FRG, an autosomal recessive or autosomal dominant disorder resulting from several different SGLT2 mutations, is characterized by persistent glucosuria in the absence of hyperglycemia or general renal tubular dysfunction. Because the majority of patients with FRG have no clinical manifestations, FRG is commonly described as a "nondisease" and is synonymous with the condition known as benign glucosuria. Even the most severe form of FRG (type O), where nonfunctioning mutations within the SGLT2 gene result in a complete absence of renal tubular glucose reabsorption, is

■ **Figure.** Renal Glucose Filtration and Reabsorption in the Proximal Tubule[17]



ATPase indicates adenosine triphosphatase; GLUT, facilitated glucose transporter; SGLT, sodium-coupled glucose cotransporter.
The major active glucose transporters present in the human kidneys are SGLT1 and SGLT2. Accounting for 90% of glucose reabsorption in the kidneys is SGLT2, which is a low-affinity, high-capacity transporter found primarily in the convoluted segment (S1) of the proximal tubule (closest to Bowman's capsule). SGLT1 is a high-affinity, low-capacity transporter that is located more distally in the straight S3 segment of the proximal tubule (further down along the nephron but before the loop of Henle), and accounts for the other 10% of renal glucose reabsorption.
Reprinted with permission from Komoroski B, Vachharajani N, Boulton D, et al. *Clin Pharmacol Ther.* 2009;85(5):520-526.

associated with a favorable prognosis. Because FRG is generally asymptomatic, affected individuals are identified through routine urinalysis.[4]

GGM, a more serious autosomal recessive disease caused by mutation of the SGLT1 transporter, is characterized by intestinal symptoms that manifest within the first few days of life and result from failure to absorb glucose and galactose from the intestinal tract. The resultant severe diarrhea and dehydration may be fatal if a glucose- and galactose-free diet is not initiated. In some patients with GGM, glucosuria is present but typically mild, while in others, no evidence of abnormal urinary glucose excretion exists, affirming the minor role of SGLT1 in renal glucose reabsorption of glucose.[4]

Gene mutations involving GLUTs are associated with more severe consequences, as these transporters are more widespread throughout the major organ systems. Compared with SGLT2 and SGLT1, which are present mostly in the renal system, GLUT2 is a widely distributed facilitative glucose transporter that has a key role in glucose homeostasis through its involvement in intestinal glucose uptake, renal reabsorption of glucose, glucosensing in the pancreas, and hepatic uptake and release of glucose.[4] Mutations of the gene encoding this protein result in Fanconi-Bickel syndrome, a rare autosomal recessive glycogen storage disease that encompasses a multitude of complications (glucose and galactose intolerance, postprandial hyperglycemia, fasting hypoglycemia, tubular nephropathy, hepatomegaly, renomegaly, rickets, and stunted growth). Because GLUT2 is involved in the tubular reabsorption of glucose, glucosuria is a feature of the nephropathy.[4]

Impact of Hyperglycemia on the Kidneys

While renal glucose reabsorption is a glucose-conserving mechanism in normal physiologic states, it is known to contribute to hyperglycemia in conditions such as T2DM.[15] Renal glucose reabsorption tends to increase with plasma glucose levels, up to plasma concentrations of 180 mg/dL to 200 mg/dL.[7] Among patients with diabetes, an excess of approximately 13 grams of glucose is taken up from the systemic circulation, of which 85% is attributed to increased renal glucose uptake.[3] Evidence suggesting a higher TmG in patients with diabetes compared with healthy controls attests to the increased state of renal glucose reabsorption seen in chronic hyperglycemia, which in turn can increase the risk of microvascular complications.[13,18] Over time, the glomeruli become damaged and are unable to filter blood efficiently and glomerular membranes leak protein (more than 50% of the protein is albumin) into the urine.[19] In patients with diabetes, the kidneys may be particularly susceptible to the effects of hyperglycemia, as many kidney cells are unable to sufficiently decrease glucose transport rates to prevent intracellular hyperglycemia in states of increased glucose concentration.[19]

Diabetic Nephropathy

Diabetes has become the most common single cause of end-stage renal disease (ESRD) in the United States and Europe; this is most likely due to several evolving factors, including an increased prevalence of T2DM, longer life spans among patients with diabetes, and better formal recognition of renal insufficiency.[20] Based on the most current (2008) US statistics from the American Diabetes Association, diabetes accounted for more than 40% of new cases of kidney failure, with 48,374 patients with diabetes beginning treatment for ESRD, and 202,290 people with diabetes-related ESRD on chronic dialysis or undergoing a kidney transplant.[20] Compared with patients with type 1 diabetes mellitus, a considerably smaller fraction of those with T2DM progress to ESRD, but due to the much higher prevalence of T2DM, these individuals constitute over half of those with diabetes on dialysis. Considerable racial/ethnic variability exists in this regard, with Native Americans, Hispanics (especially Mexican Americans), and African Americans at much greater risk of developing ESRD than non-Hispanic whites with T2DM.[20]

Dialysis is a very expensive therapy, costing more than $50,000 per patient per year. Total medical spending for the approximately 400,000 patients with ESRD (representing those with and without diabetes) was $22.8 billion in 2001, an almost 3-fold increase over the 1991 to 2001 decade. ESRD spending represents 6.4% of the total Medicare budget, a 33% increase from 4.8% in 1991. The epidemic growth in ESRD cases has led to skyrocketing utilization of healthcare resources.[21]

The earliest clinical evidence of nephropathy is the appearance of low, but abnormal, levels (≥30 mg/day or 20 µg/min) of albumin in the urine (referred to as microalbuminuria).[20] Although the course for each patient with T2DM is different, once albumin is detected in the urine, the chance of progression to more persistent albuminuria, progressive decline in GFR, raised arterial blood pressure, and increased cardiovascular morbidity and mortality is increased. Since undetected T2DM may be present for many years, a higher proportion of individuals with T2DM (vs type 1 diabetes mellitus) have microalbuminuria and overt nephropathy shortly after diagnosis. Without specific interventions, 20% to 40% of patients with T2DM and microalbuminuria progress to overt nephropathy; however, within 20 years of onset of overt nephropathy, only 20% will have progressed to ESRD.[20] This may be attributable to the greater risk of dying from associated coronary artery disease than progressing to ESRD among the older diabetic population. As interventions for coronary artery disease continue to improve, however, more patients with T2DM may survive long enough to develop renal failure.[20]

Increasing evidence demonstrates that the onset and course of diabetic nephropathy may be significantly altered by several interventions (eg, tight glucose control, use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), all of which have their greatest impact if instituted early. As such, annual screening for microalbuminuria is critical since it leads to early identification of nephropathy. Well-known data from the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study established that intensive glycemic control may significantly reduce the risk of developing microalbuminuria and overt nephropathy.[20] Recent research (eg, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE] trial) offers more perspective on the effects of tight glucose control and reduction of nephropathy.[22] ADVANCE evaluated progression to major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy) in 11,140 patients with T2DM randomly assigned to undergo standard or intensive glucose control (glycated hemoglobin level ≤6.5%). After a median of 5 years, intensive glucose control produced a 10% relative reduction in the combined outcome of major

macrovascular and microvascular events, primarily as a result of a 21% relative reduction in the risk of developing new or worsening nephropathy. The intensive glucose control group was also associated with a 9% reduction in new onset microalbuminuria, but a higher incidence of severe hypoglycemia (2.7% vs 1.5% in the standard control group). The observed reduction in nephropathy is important, since indices of renal impairment are strongly associated with future risk of major vascular events, ESRD, and death in patients with diabetes.

Conclusion

The regulation of glucose production, uptake, reabsorption, and elimination is handled by several organs, most notably (historically) the pancreas and liver. While not traditionally discussed, the kidneys' contributions to maintaining glucose homeostasis are multifaceted and include such functions as gluconeogenesis and glucose reabsorption, the latter being mediated by active (SGLT) and passive (GLUT) transporters. Under normal circumstances, glucose filtered by glomeruli is completely reabsorbed, but in conditions of hyperglycemia or reduced resorptive capacity, glucosuria may occur. In hyperglycemia, the kidneys may play an exacerbating role by reabsorbing excess glucose, ultimately contributing to chronic hyperglycemia, and subsequently to pancreatic β-cell failure, insulin resistance, and decreased glucose uptake. Hyperglycemia in turn detrimentally affects the kidneys by damaging glomeruli, ultimately causing microalbuminuria and nephropathy. Knowledge of the kidneys' role in glucose homeostasis and the effect of glucose dysregulation on the kidneys is critical to optimal management of T2DM and prevention of associated renal complications.

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