AJKD

Perspective

Sodium/Glucose Cotransporter 2 Inhibitors and Prevention of Diabetic Nephropathy: Targeting the Renal Tubule in Diabetes

Luca De Nicola, MD, PhD,[1] Francis B. Gabbai, MD,[2] Maria Elena Liberti, MD,[1] Adelia Sagliocca, MD,[1] Giuseppe Conte, MD,[1] and Roberto Minutolo, MD, PhD[1]

Optimal prevention and treatment of chronic kidney disease in diabetes requires implementing therapies that specifically interfere with the pathogenesis of diabetic nephropathy. In this regard, significant attention has been given to alterations of the proximal tubule and resulting changes in glomerular filtration rate. At the onset of diabetes mellitus, hyperglycemia causes increases in proximal tubular reabsorption secondary to induction of tubular growth with associated increases in sodium/glucose cotransport. The increase in proximal reabsorption leads to a decrease in solute load to the macula densa, deactivation of the tubuloglomerular feedback, and increases in glomerular filtration rate. Because glomerular hyperfiltration currently is recognized as a risk factor for progression of kidney disease in diabetic patients, limiting proximal tubular reabsorption constitutes a potential target to reduce hyperfiltration. The recent introduction of sodium/glucose cotransporter 2 (SGLT2) inhibitors opens new therapeutic perspectives for this high-risk patient population. Experimental studies have shown that these new agents attenuate the progressive nature of diabetic nephropathy by blood glucose–dependent and –independent mechanisms. SGLT2 inhibition may prevent glomerular hyperfiltration independent of the effect of lowering blood glucose levels while limiting kidney growth, inflammation, and albuminuria through reductions in blood glucose levels. Clinical data for the potential role of the proximal tubule in the pathophysiology of diabetic nephropathy and the nephroprotective effects of SGLT2 inhibitors currently are limited compared to the more extensive experimental literature. We review the evidence supporting this working hypothesis by integrating the experimental findings with the available clinical data.

Am J Kidney Dis. ■(■):■-■. © *2014 by the National Kidney Foundation, Inc.*

INDEX WORDS: Diabetes mellitus (DM); diabetic nephropathy (DN); hyperfiltration; glomerular filtration rate (GFR); proximal tubule; sodium/glucose cotransport; sodium/glucose cotransporter 2 (SGLT2); SGLT2 inhibitor; canagliflozin; dapagliflozin.

Diabetes mellitus (DM) is a major public health problem worldwide. The prevalence of type 2 DM is increasing exponentially; it is estimated that more than 400 million people will have DM by 2030.[1] Among the various complications of DM, diabetic nephropathy (DN) is considered a major threat because it affects approximately one-third of all diabetic individuals and is a main cause of mortality and a leading cause of end-stage renal disease.[2] DN is characterized by persistent albuminuria, decline in glomerular filtration rate (GFR), increasing blood pressure (BP), and high cardiovascular (CV) risk.

Patients with non–dialysis-dependent type 2 DN, a condition frequently encountered in endocrine/diabetes and nephrology clinics, benefit from strict cooperation between the 2 specialties to improve prognosis.[3,4] Optimal prevention and treatment of chronic kidney disease (CKD) in patients with DM requires implementing therapies that specifically interfere with the pathogenesis of DN.[5] In this regard, significant attention has been given to the role of the proximal tubule.[6,7] It is well known that the dimensions and function of the proximal tubule increase in response to higher glucose load. These changes have been linked to the increase in GFR, or so-called diabetic hyperfiltration. The development of new antidiabetic agents, such as inhibitors of sodium/glucose cotransporter 2 (SGLT2; encoded by the *SLC5A2* gene), has raised the intriguing possibility of new tools to prevent DN. Data for the role of increased tubular reabsorption in the pathophysiology of human DN are limited compared to the more robust experimental literature. We review the information supporting this hypothesis by integrating the experimental findings with the available clinical data.

EARLY CHANGES IN THE DIABETIC KIDNEY

Glomerular Hyperfiltration

In the setting of DM, hyperglycemia is accompanied by an increase in GFR. Investigators have proposed several mechanisms to explain diabetic hyperfiltration,

From the [1]Nephrology Division, Second University of Naples-Med School, Naples, Italy; and [2]Department of Medicine, Veterans Administration San Diego Healthcare System-University of California at San Diego Medical School, San Diego, CA.

Received October 25, 2013. Accepted in revised form February 5, 2014.

Address correspondence to Luca De Nicola, MD, PhD, Nephrology Division, Second University of Naples-Med School, P.O. S.M.D.P Incurabili, Via Maria Longo 50, 80138 Napoli, Italy. E-mail: luca.denicola@unina2.it

0272-6386/$36.00

http://dx.doi.org/10.1053/j.ajkd.2014.02.010

including impaired constriction of the afferent arteriole.[6-8] These hemodynamic changes have been associated with activation of neurogenic, hormonal, and myogenic factors (known as the hemodynamic hypothesis). However, increased proximal tubular reabsorption also has been shown within the spectrum of the early changes observed in diabetic kidneys, suggesting an alternative hypothesis to explain the increase in GFR (known as the tubular hypothesis).

Under normal and pathophysiologic conditions, glomeruli and tubules are functionally linked to ensure maintenance of adequate extracellular volume and consequently systemic perfusion.[9] Two mechanisms are involved in this process. Glomerulotubular balance modulates proximal tubular reabsorption according to changes in GFR in order to guarantee a constant percentage of tubular reabsorption of filtered solutes. Any increase in GFR determines an increase in proximal tubular reabsorption, and vice versa. The mechanism mainly depends on parallel changes in peritubular capillary oncotic pressure that accompany changes in filtration fraction. However, glomerulotubular balance is not fully efficient in maintaining fractional reabsorption constant.

Due to the limitation of glomerulotubular balance, part of any change in GFR will pass along the nephron, eliciting the tubuloglomerular feedback response, which will counteract some of the original disturbance. Tubuloglomerular feedback is driven by signals directly generated at the level of the macula densa whereby changes in sodium chloride concentration in tubular fluid cause opposite changes in single-nephron GFR (Fig 1). When a primary reduction in proximal tubular reabsorption ensues, the amount of sodium chloride in the thick ascending limb of Henle and the first part of the distal tubule, the so-called distal delivery of sodium chloride, increases, which in turn leads to a decrease in GFR. Conversely, a reduction in distal delivery driven by increased reabsorption in the proximal tubule induces an increase in single-nephron GFR. Tubuloglomerular feedback is continuously active and modulates the tone of glomerular afferent resistance through the release of adenosine, a vasoconstrictive substance. Tubuloglomerular feedback and glomerulotubular balance maintain relatively constant distal salt delivery and sodium excretion when GFR increases. The efficiency of the 2 mechanisms ensures the optimal defense against volume depletion because if the primum movens is of a vascular nature, there is a tubular adaptation (glomerulotubular balance), whereas if the primum movens is of tubular origin, a glomerular adaptation (tubuloglomerular feedback) ensues.

In the early stages of diabetes, tubuloglomerular feedback has a major role. In diabetic rats, hyperglycemia

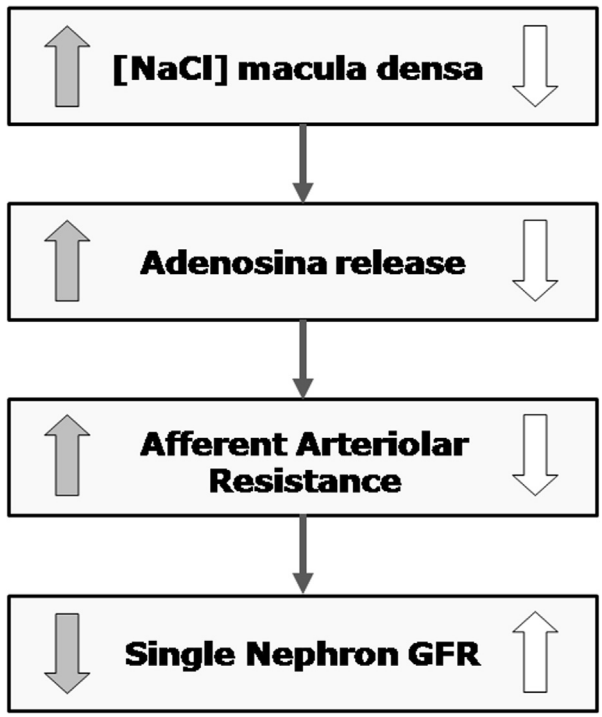

Figure 1. Physiology of tubuloglomerular feedback. Abbreviations: NaCl, sodium chloride; GFR, glomerular filtration rate.

induces an increase in proximal tubular reabsorption due to proximal tubular hypertrophy and a consequent increase in sodium/glucose cotransport. The reduction in solute delivery to the macula densa thereby decreases tubuloglomerular feedback activity with a consequent increase in single-nephron GFR.[7]

According to the hemodynamic hypothesis of hyperfiltration, an excess of total-body sodium in patients with DM was proposed as a contributor to the renal vasodilatation possibly by suppressing vasoconstricting neurohormonal systems. Such a hypothesis was not supported by results of a randomized trial in patients with uncomplicated insulin-dependent DM.[10] In that study, investigators measured GFR and renal plasma flow in patients with DM and in age- and sex-matched controls consuming a normal- (200 mmol/d) and low- (20 mmol/d) sodium diet. A normal-sodium diet was associated with lower renal vascular resistance and higher GFR in patients. Unexpectedly, salt restriction did not correct kidney hyperperfusion, but exacerbated it. These alterations were specific to DM; no significant changes in response to variations in dietary salt intake were observed in controls. Experimental studies have explained the potential mechanism of this "salt paradox" in DM by demonstrating that proximal tubular reabsorption is more sensitive to variations in dietary salt in this model, with an abnormal tendency for GFR to vary inversely with sodium intake.[6,7,11]