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To Evaluate Glucose-Lowering Therapy for the Functional State of the Kidneys in Patients with Type 2 Diabetes Mellitus

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Abstract: To prevent the progression of CKD, careful management of metabolic disorders requires adequate glycemic control in DN to help improve quality of life and reduce disability. Regulation of elevated glucose levels in people with type 2 diabetes mellitus and CKD is carried out individually for each patient, taking into account such parameters as: the functional state of the kidneys, life expectancy, the likelihood of hypoglycemic conditions and accompanying diseases.

Keywords: CKD, diabetes, diabetic nephropathy, hypoglycemic.

Current therapy aimed at slowing the progression of diabetic nephropathy includes intensive glycemic and optimal blood pressure control, reduction of proteinuria and albuminuria, interruption of the renin-angiotensin-aldosterone system through the use of angiotensin-converting enzyme inhibitors and angiotensin-1 receptor blockers, along with modification of diet and medication, lowering cholesterol levels [1]. However, the kidney protection provided by these therapeutic methods is incomplete.

The pathogenesis of diabetic nephropathy (DN) is multifactorial, complex and not fully understood. Evidence of this is that a growing number of studies indicate that some patients with diabetes do not experience the same evolution that was identified at the time: for example, some often experience a significant initial decline in glomerular filtration rate, while others microalbuminuria decreases spontaneously [2]. Chronic kidney disease may be accompanied rather than preceded by macroalbuminuria, or it may develop in patients with microalbuminuria or even in patients with normal albuminuria [3].

In the setting of diabetes, metabolic disturbances and hemodynamic changes, especially activation of the renin-angiotensin system, trigger a series of cellular signaling cascades that mediate cellular responses through the activation of key transcription factors. In response to such signals, renal cells, such as tubular epithelial cells, podocytes and mesangial cells, can produce chemokines, growth factors and profibrotic cytokines [4]. These responses contribute to a cycle of inflammation, oxidative stress, cellular damage, progressive fibrosis, and decreased glomerular filtration rate. Loss of podocytes, endothelial dysfunction, changes in the glomerular basement membrane and tubular damage contribute to increased proteinuria during the development and progression of nephropathy [4]. Intensive control of glycemia and blood pressure is effective in both preventing the onset and reducing the progression of albuminuria and DN [5,6].

Despite the positive results of the standard principle of caution for DN, excluding the regulation of carbohydrate metabolism containing RAAS suppressors, stabilization of blood pressure, weight, as well as fat metabolism values in people with DN, the development and progress of CKD, as before, cannot be excluded [7]. This fact indicates the need for new effective therapeutic therapies to better delay the development of DN.

Most likely, positive renal effects of drugs that have a positive effect on less known factors in the development of DN (impaired endothelial function, decreased insulin sensitivity in podocytes, tubulointerstitial defects, inflammatory processes, oxidative stress, imbalance of vasoactive substances, changes in autonomic nervous activity , anemia, etc.) [8]. As a result, if we have protective

qualities of the kidneys in the SSP groups, in particular in those that have a chain of influence at the genetic level on DN, in addition to this, additional metabolic benefits, which today are the main objectives of the search in experimental and clinical studies.

The United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive blood glucose control with sulfonylureas or insulin reduced the risk of microvascular complications [9]. And more recent randomized controlled trials in patients with type 2 diabetes have yielded mixed results. The ADVANCE (Action in Diabetes and Vascular Disease) study showed that intensive glycemic control reduces albuminuria, nephropathy and the need for dialysis. Similarly, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial showed significantly lower rates of albuminuria (but not more severe nephropathy) in the intensive glycemic control group [10]. It is unknown whether these effects would have affected microvascular and, perhaps more importantly, macrovascular protection, as the study was not designed to evaluate these long-term outcomes.

In the Action for Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, a combined approach of routine blood pressure lowering and intensive glucose control resulted in a significant reduction in major renal complications and mortality [11]. The lack of interaction between blood pressure lowering and intensive glucose control indicates that the effects of the two interventions were independent. However, the study was unable to demonstrate individual effects, as well as a positive effect of glycoside on the kidneys [67; p.359-368].

A recent review by Chan and Tang clearly describes two major unmet needs in nephrology practice [12]: (1) limited effectiveness and/or low tolerability of traditional nephroprotective interventions, as demonstrated in 23 landmark randomized trials (RCTs). in patients with diabetes mellitus with and without CKD; (2) lack of clinical benefit in patients of new drugs with nephroprotective efficacy proven in experimental models. Thus, RAS inhibitor therapy remains the main nephroprotective intervention, which, unfortunately, still leaves 30 to 50% of patients at high risk of developing end-stage renal disease (ESRD). Accordingly, administration of iSGLT2 appears to be an important step towards reducing the burden of CKD. The beneficial effects of SGLT2i on the kidneys were first shown in the EMPAREG, CANVAS and DECLARE cardiovascular trials (CVOT). These studies were initially aimed at assessing cardiovascular safety in patients with type 2 diabetes mellitus (T2DM) with renal outcomes as a secondary endpoint [13]. The vast majority of patients were at low risk of renal failure and little change in renal function was observed. An important step forward was the CREDENCE study, which was specifically designed and therefore valid for assessing the progression of kidney disease in patients with type 2 diabetes with overt CKD.

The mechanism of diabetic kidney damage is complex, involving hemodynamic and non-hemodynamic factors, activated primarily by permanent hyperglycemia [14]. Based on the multifactorial pathophysiology of diabetic kidney disease (DKD) and the striking renal protection associated with SGLT-2, several mechanisms have been proposed to explain the remarkable renal benefits of this new class of agents. Systemic effects that should be considered include reductions in extracellular volume, total body sodium, and arterial stiffness, resulting in decreased blood pressure (BP) and albuminuria [15]. In addition, in addition to the hypoglycemic effect, SGLT-2 may improve endothelial function through several mechanisms, including weight loss and reduction in body fat due to daily energy losses of up to 300 kcal (due to glucosuria 70–80 g/day), decreased resistance to insulin and a decrease in uric acid levels;. Newer evidence suggests a role for reduced oxidative stress and endoplasmic reticulum stress due to increased autophagy flux in podocytes and renal tubules.

Notably, the reduction in glucose reabsorption by SGLT-2 is associated with significant changes in renal hemodynamics. Micropuncture studies performed in hyperglycemic diabetic rats have shown that poor glucose control is associated with increased GFR (hyperfiltration) at the level of the entire kidney and individual nephron. The presence of hyperfiltration is currently recognized as the main mechanism of induced kidney damage in patients with type 2 diabetes and in experimental animals [16]. Based on renal micropuncture studies, Vallon, Thomson, and Blanz proposed a “tubulocentric” hypothesis to explain the hemodynamic responses of the kidneys to increased glucose load, as well as the beneficial

effects of SGLT-2 inhibitors. It is known that diabetes promotes hypertrophy of proximal tubule cells with a subsequent increase in the expression of SGLT-2, which leads to an increase in reabsorption in the proximal tubules and a decrease in the delivery of sodium chloride to the distal sections. Recent experimental evidence has shown that glucose delivery to the macula densa also activates SGLT-2 receptors located in this structure, with subsequent stimulation of nitric oxide production through neuronal nitric oxide synthase. The generation of such a potent vasodilator promotes afferent cell dilatation and increased nephron filtration, providing an additional mechanism underlying the modulation of glomerular afferent resistance under conditions of poorly controlled glycemia. SGLT-2 restores the speed of blood flow in the proximal tubules, counteracting "hyper-reabsorption". Consequently, SGLT-2 ameliorates glomerular hypertension and hyperfiltration, thereby reducing glomerular barotrauma and albuminuria. It should be noted that a potential additional consequence of attenuating hyperfiltration is a reduction in oxygen (O2) demand for active tubular transport of solutes, primarily sodium, with improved oxygenation of renal tissue and prevention of fibrosis [17,18]. However, experimental and a number of clinical studies demonstrate the potential nephroprotective capabilities of gliflozin in relation to regression of renal morphological changes and reduction of albuminuria.

Conclusion: Thus, a review of modern literature showed that the prevalence of diabetes is growing every year, and, as a result, the number of patients with vascular complications of diabetes, which lead to early disability and mortality of patients, is increasing. Diabetic kidney damage with the development of end-stage chronic renal failure poses a great threat to life. Contemporary management of type 2 diabetes involves multiple therapeutic targets aimed at preventing micro- and macrovascular complications of this disease.

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